Technology Assessment

Technology Assessment Program

Technology Assessment of Molecular Pathology Testing for the Estimation of Prognosis for Common Cancers

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Technology Assessment of Molecular Pathology Testing for the Estimation of Prognosis for Common Cancers

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Peer Reviewers

We wish to acknowledge individuals listed below for their review of this report. This report has been reviewed in draft form by individuals chosen for their expertise and diverse perspectives. The purpose of the review was to provide candid, objective, and critical comments for consideration by the EPC in preparation of the final report. Synthesis of the scientific literature presented here does not necessarily represent the views of individual reviewers.

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Structured Abstract

Structured Abstract

Objectives: To conduct a systematic review and meta-analysis assessing the prognostic value and test performance (analytic validity, clinical validity, clinical utility, and harms) associated with 11 prognostic molecular pathology tests. Many of these tests are indicated for prediction of therapeutic responses, but this review focuses on their potential use as prognostic factors. Our overarching question was whether there is direct evidence that the addition of these molecular pathology tests changed physician decisionmaking and improved outcomes for adult patients.

We evaluated the following tests: microsatellite instability assessment by polymerase chain reaction (PCR) for colorectal cancer (CRC), MLH1 promoter methylation for CRC, *KRAS* mutation testing for CRC, *BRAF* mutation testing for CRC, Oncotype DX Colon mRNA expression for CRC, Oncotype DX Breast mRNA expression for breast cancer, MammaPrint mRNA expression for breast cancer, *ALK* cytogenetics for lung cancer, *EGFR* mutation testing for lung cancer, *KRAS* mutation testing for lung cancer, and UroVysion cytogenetics for urinary bladder cancer.

Data Sources: PubMed®, the Cochrane Library, and EMBASE® (through November 2013); reference lists of pertinent review articles and included studies, test developers' Web sites, ClinicalTrials.gov, the Food and Drug Administration (FDA) Web site, Health Services Research Projects in Progress, the European Union Clinical Trials Register, the College of American Pathologists (CAP), and data submitted by companies that developed the tests.

Review Methods: Two investigators independently selected, extracted data from, and rated risk of bias of each study. For clinical validity, we conducted meta-analyses to estimate weighted summary hazard ratios when three or more studies reported an eligible outcome. For the other review questions, we did not find sufficient data to conduct meta-analyses. Therefore, we synthesized the information qualitatively. We graded strength of evidence based on established guidance.

Results: Evidence from multiple studies supports associations between test results and prognosis, with added value beyond known independent prognostic factors, for MammaPrint, Oncotype DX Breast, *KRAS* mutation testing for lung cancer, *BRAF* and *KRAS* mutation testing for CRC, and microsatellite instability for CRC for at least one of our included outcomes (i.e., risk of recurrence, cancer-specific survival, or overall survival). Although UroVysion is marketed as a diagnostic rather than a prognostic test, limited evidence from two small studies (total N=168) rated as low or medium risk of bias supported associations between test result and prognosis for risk of recurrence. We found no studies that directly assessed the impact of a test of interest on both physician decision-making and downstream health outcomes to establish clinical utility. We attempted to construct an indirect chain of evidence to answer the overarching question, but we were unable to do so. Even in the cases where the tests seemed to add value in determining prognosis (i.e., evidence of clinical validity), we found no evidence that using the test was related to improved outcomes for patients. However, for impact of test use on treatment decisions, we found moderate strength of evidence that Oncotype DX Breast leads to changes in treatment decisions. Although the decision changes were observed in both directions for

individual patients, studies consistently showed an overall shift to less-intensive treatment recommendations as a result of using Oncotype DX Breast, with fewer recommendations for chemotherapy (and less exposure to potential harms of chemotherapy).

Limitations: We were not able to directly address the prognostic value of these tests for the Medicare population. There were several studies that included patients from the Medicare age group and although the impact of these tests were not analyzed with specific reference to this population, we did not come across any evidence that suggested that the prognostic value of these tests would be different for the Medicare population.

Conclusions: Modest evidence supports added prognostic value (i.e., clinical validity) for over half of the tests evaluated, and that Oncotype DX Breast leads to changes in treatment decisions, but we found no evidence to determine whether using the tests to estimate prognosis leads to improved outcomes for patients.

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Executive Summary

Background

Molecular pathology tests that identify pathogenic mutations and cytogenetic translocations help us define the molecular subtypes of common cancers. Because several of these acquired mutations/translocations may predict response to specific therapies, screening tests for "targetable" mutations are now commonly available in clinical laboratory improvement amendments (CLIA)-approved clinical labs. It is unclear whether these test results can also serve as independent prognostic factors. This review aims to clarify the value of certain molecular pathology tests for improving our estimates of prognosis for common cancers (breast, lung, colon, urinary bladder) affecting Medicare beneficiaries. The main purpose of this review is to determine whether these tests improve estimation of prognosis (for recurrence), affect physician decision making, and/or improve clinical outcomes when compared with traditional assessment of prognosis of recurrence. These genetic tests are used in two different contexts. In one, the tests are used in a specific context of a diagnostic/therapy combination, where the diagnostic test is being used to predict response to a very specific treatment. In the second context, the genetic tests are used to estimate the patient's prognosis, and physicians use this prognostic information to choose from a variety of different treatment options. CMS requested this report to evaluate the second context. Therefore, studies that evaluate specific diagnostic/therapy combinations are excluded from this report

The following tests are under consideration for this assessment and apply to all Key Questions (KQs): microsatellite instability (MSI) for colorectal cancer (CRC), MLH1 promoter methylation for CRC, *KRAS* mutations for CRC, *BRAF* mutations for CRC, Oncotype DX Colon mRNA expression for CRC, Oncotype DX Breast mRNA expression for breast cancer, MammaPrint mRNA expression for breast cancer, *ALK* cytogenetics for lung cancer, *EGFR* mutations for lung cancer, *KRAS* mutations for lung cancer, and UroVysion cytogenetics for urinary bladder cancer.

Our overarching question was whether there is direct evidence that the addition of the results of these molecular pathology tests to traditional prognostic factors changed physician decisionmaking and improved clinical outcomes for adult patients. We also examined analytic validity, clinical validity and utility, and any harms to patients associated with these tests. In this review, we address the following KQs:

KQ 1. Overarching Question: Is there direct evidence that the addition of the specified molecular pathology tests used alone or in combination with traditional prognostic factors changes physician decisionmaking and improves outcomes for adult patients with CRC, breast, lung, or bladder cancer compared with the use of traditional factors to predict risk of recurrence (RR) for adults with these cancers?

KQ 2. Analytic Validity: Does existing evidence establish the technical accuracy and reliability of these tests for detecting the relevant molecular analytes?

KQ 3. Clinical Validity: Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4. Clinical Utility: Does existing evidence support clinical utility of the molecular pathology tests?

KQ 4a. What is the evidence that the prognostic information provided by the molecular pathology tests modifies physician decisions regarding use of adjuvant antineoplastic chemo- and/or radiotherapy, enhanced diagnostic testing for recurrence, and/or surgery among adult patients with malignant tumors?

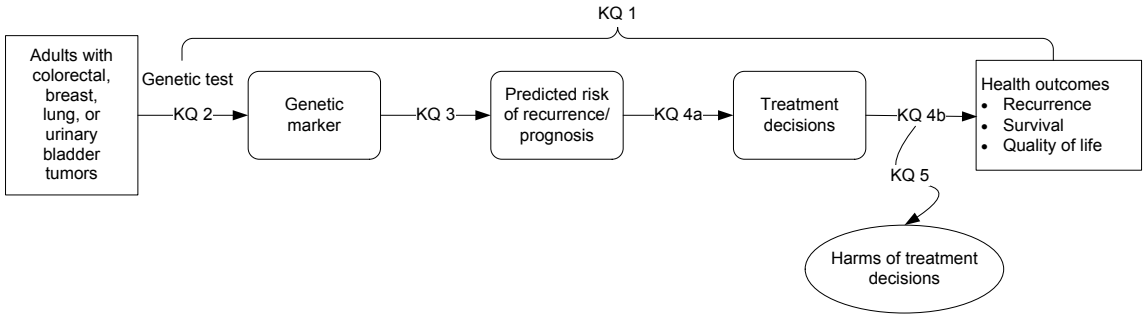
KQ 4b. What is the evidence that modified decisions lead to improved outcomes, including patient-centered outcomes such as improved quality of life, reduced disease recurrence, increased overall survival (OS) or disease-free survival (DFS), or reduced therapeutic side effects?

KQ 5. What are the harms associated with treatment decisions that are informed by the molecular pathology tests?

Analytic Framework

We developed an analytic framework to guide the systematic review process (Figure A).

Figure A. Analytic framework



Abbreviation: KQ = Key Question.

Methods

Literature Search Strategy

We searched PubMed®, the Cochrane Library, and EMBASE® for English-language, adult, and human-only studies published from inception through November 2013. Searches were run by an experienced Evidence-based Practice Center (EPC) librarian and were peer reviewed by another EPC librarian. We manually searched reference lists of pertinent review articles and studies meeting our inclusion criteria to look for any relevant citations that our searches might have missed. We searched for unpublished studies relevant to this review using test developers' Web sites, ClinicalTrials.gov, the Food and Drug Administration Web site, Health Services Research Projects in Progress, and the European Union Clinical Trials Register. In addition, we requested information from the College of American Pathologists (CAP) and from relevant companies, asking for data that they believe should be considered for the review.

Eligibility Criteria

We developed eligibility criteria for Populations, Interventions (i.e., tests for this report), Comparators, Outcomes, Timing, Settings (PICOTS), and study designs. Briefly, we included studies of adult patients with one of the cancer types of interest that evaluated an eligible molecular pathology test (listed in the Background). For KQs 1, 4, and 5, we included studies that compare at least 1 of the 11 molecular pathology tests plus standard prognostic factors with the standard prognostic factors alone to determine whether the molecular pathology test adds independent prognostic value (benefit) or introduces additional harms (KQ 5). Studies that compare an eligible molecular pathology test alone with standard prognostic factors were also eligible for inclusion. For KQ 2 (analytic validity), we included studies of test performance, including intra/interlab reproducibility. For KQ 3 (clinical validity), we included studies comparing patients with different test results (e.g., those with a mutation versus those who are wild-type) to establish prognostic value, with a multivariate analysis to adjust for known factors. To inform whether these molecular pathology tests *add value* above standard prognostic factors, we required that results were either adjusted for known prognostic factors or were specifically addressed in other ways, such as through inclusion/exclusion criteria of the study or stratification.

We required studies to report one of the following outcomes: for KQ 1, direct evidence of the impact of the test on physician decisionmaking and also on health outcomes (OS, DFS, time to recurrence, or quality of life); for KQ 2, tissue sample acceptance/rejection criteria, test performance, intra- and interlab reproducibility for the same specimen, lower limit of detection in admixtures of carcinoma and normal cells, and quality controls; for KQ 3, assessment of added prognostic value (i.e., by assessing discrimination, calibration, or association of test results with recurrence) beyond known independent prognostic factors for recurrence, cancer-specific survival (CSS), and overall survival (OS); for KQ 4a, modification of physician decisions about treatment; for KQ 4b, health outcomes (OS, DFS, time to recurrence, quality of life); and for KQ 5, adverse effects of tests, adverse effects of adjuvant therapy, and decreased quality of life.

We did not include studies focused on patients with advanced/metastatic cancer or studies focused on predicting response to treatments (e.g., studies focused on response to gefitinib for people with *EGFR*-mutant advanced lung adenocarcinomas). Progression-free survival was not an eligible outcome. Additional details of the eligibility criteria, including eligible study designs, are provided in the full technical report.

Study Selection

Two members of the research team independently reviewed each title and abstract identified through searches for eligibility. Studies marked for possible inclusion by either reviewer and those that lacked adequate information to determine eligibility underwent a full-text review. Two members of the research team independently reviewed each full-text article to determine eligibility. If the reviewers disagreed, they resolved conflicts by discussion and consensus or by consulting a third member of the review team.

Data Extraction

We designed and used structured data extraction forms to gather pertinent information from each article; this included characteristics of study populations, settings, interventions, comparators, study designs, methods, and results. Trained reviewers extracted the relevant data

from each included article. All data extractions were reviewed for completeness and accuracy by a second member of the team.

Risk-of-Bias Assessment of Individual Studies

We assessed the risk of bias (RoB) (internal validity) using an approach supported by the *Methods Guide for Medical Test Reviews*.[1] For studies of analytic validity, we considered the potential for bias due to flaws in the sample selection, testing protocol, reference standards, verification procedures, interpretation, and analysis. We used the questions relevant for prognostic tests from the QUADAS-2[2,3] (which was developed for diagnostic tests) for assessing risk of relevant biases. For studies of clinical validity and clinical utility, we assessed the potential for selection bias, confounding, performance bias, attrition bias, and detection bias. We assessed these biases using relevant questions and predefined criteria based on guidance from the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* and the RTI Question Bank.[4] We rated RoB for each study as low, medium, high, or unclear. Two independent reviewers assessed the RoB for each study. Disagreements between the two reviewers were resolved by discussion and consensus or by a third member of the team.

Data Synthesis

For clinical validity (KQ 3), we conducted meta-analyses using techniques described in Hedges and Vevea.[4] We estimated summary hazard ratios (HRs) for outcomes (for any given test-cancer pair) with three or more independent adjusted HR estimates. We tested the null hypothesis of homogeneity of effect sizes across the studies[4,5] for each of the outcomes. If the null hypothesis was rejected at a significance level of 0.05, the summary HR was estimated using a random effects model; if not, it was estimated using a fixed effects model. In both cases, the inverse of the variance was used to estimate a weighted summary HR.

For the other KQs, we did not find sufficient data to conduct meta-analyses. Therefore, we synthesized the information qualitatively, in tabular and narrative format.

We did not include studies with a high or unclear RoB in our main analyses/main data syntheses.

Strength of the Body of Evidence

We graded the strength of evidence (SOE) as high, moderate, low, or insufficient based on the guidance established for the EPC Program.[6,7] Developed to grade the overall strength of a body of evidence, this approach incorporates four key domains: RoB (includes study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers other optional domains. For each test being evaluated in this review, two reviewers assessed each domain for each key outcome and determined an overall SOE grade based on domain ratings. In the event of disagreements on the domain or overall grade, they resolved differences by consensus discussion or by consulting with a third investigator.

We attempted to find studies that directly address the overarching question (KQ 1). If we did not find adequate direct evidence addressing the overarching question, we attempted to construct an indirect chain of evidence (using studies identified for the other KQs). We graded the SOE separately for analytic validity and for evidence on our overarching KQ. For analytic validity, we graded the SOE for the following: sensitivity and specificity, positive and negative predictive

value, and intra/interlab reproducibility. For evidence on the overarching KQ, we graded the SOE for the following outcomes: RR, CSS, OS, and decisions about treatment.

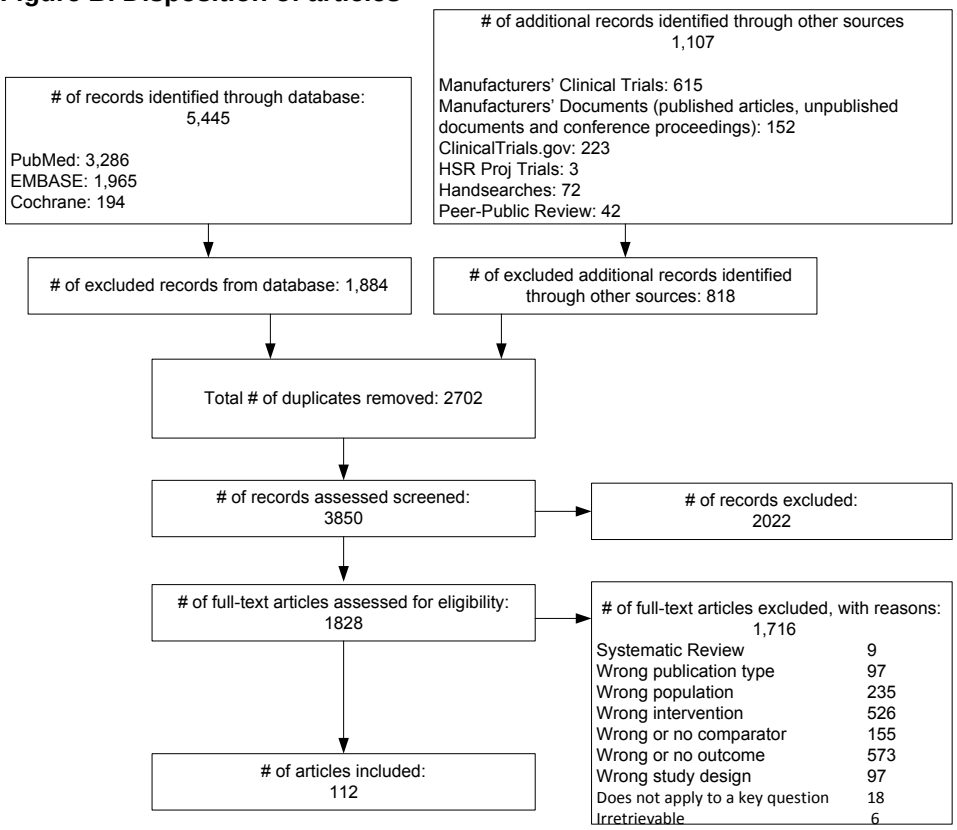
Applicability

We assessed applicability of the evidence following guidance from the *Methods Guide for Comparative Effectiveness Reviews*.[5,8] We used the PICOTS framework to explore factors that affect applicability.

Results

We included 112 publications reporting on tests of interest for the 4 cancers (Figure B).

Figure B. Disposition of articles



We found no studies that directly addressed our overarching questions (KQ 1) (i.e., no study directly assessed the impact of a molecular pathology test result of interest on both physician decisionmaking and downstream health outcomes). We attempted to construct an indirect chain of evidence to answer the overarching question, but no studies addressed whether modified decisions lead to improved health outcomes (KQ 4b, clinical utility), so we were unable to do so. The furthest downstream evidence that we found addressed whether prognostic information provided by the molecular pathology tests modifies treatment decisions (KQ 4a).

The majority of studies meeting inclusion criteria for our review focused on clinical validity (KQ 3), and they evaluated associations between prognostic tests and outcomes. For two tests, MammaPrint and Oncotype DX Breast, we found studies rated as low or medium RoB

addressing whether prognostic information provided by their mRNA abundance risk stratification tests modified treatment decisions (KQ 4a).

Analytic Validity

Included studies provide some evidence regarding analytic validity (KQ 2) for all of the included tests. Data from included studies was supplemented with proficiency tests results provided by the College of American Pathologists (CAP) for five tests for which this data was available.

Data on intra- and interlab reproducibility is available in the primary literature and through national organization proficiency testing programs. Beau-Faller[9] found high interlab reproducibility for EGFR and KRAS mutation testing. Cronin's[10] group at Genomic Health (Clin Chem 2007) found high intralab reproducibility for Oncotype quantitative RT-PCR mRNA abundance measurements relevant to the Oncotype DX tests for breast and colon carcinoma. The College of American Pathologists sends proficiency test unknowns to CLIA-approved US clinical laboratories or International clinical laboratories, an excellent mechanism for assessing nationwide interlab reproducibility. The three most recent surveys for each of these analytes showed average accuracy rates of 95 percent for EGFR (413/438), 98 percent for *KRAS* (602/612), 99 percent for *BRAF* (528/533), 99 percent for MSI (288/291), and 99 percent for UroVysion (552/555) (data presented are percentage of labs with correct results; and number with correct results/total number of labs that tested in parentheses).[11-15]

Clinical Validity

Included studies provided some evidence on clinical validity for 9 of the included tests, adjusted for known prognostic factors (Table A). Evidence from multiple studies supports clinical validity, with added value beyond traditional prognostic factors, for MammaPrint, Oncotype DX Breast, *KRAS* mutation testing for lung cancer, *BRAF* mutation testing for CRC, *KRAS* mutation testing for CRC, and MSI for CRC for at least one of our included outcomes (i.e., RR, CSS, or OS). For UroVysion, limited evidence from 2 small studies (total N=168) rated as low or medium RoB supported prognostic value for RR. *EGFR* lung cancer did not add prognostic value to the traditional factors used to determine prognosis. For CRC, evidence did not adequately support added prognostic value for Oncotype DX Colon. The metric used to assess the clinical validity of the test for recurrence, CSS, or OS in all of these studies was the HR. HRs in this report range from 0.57 to 3.93. If the test is noninformative, we expect that the probability of experiencing the end point would be the same for either group, with an HR of 1. If the HR is greater than 1, the probability of the endpoint is higher in the group with the higher hazard. If the HR is lower than 1, the probability of experiencing the endpoint is lower in the group with the lower hazard. For example, an HR of 2 for CSS indicates that one group (e.g., those with high risk results for Oncotype DX Breast) has twice the rate per unit of time as the comparison group (e.g., those with low-risk test results).

Table A. Summary of findings on clinical validity

Test: Cancer	Outcome	N studies; N subjects	Results Effect Size (95% CI)	Evidence from Multiple Studies Supports Association between Test Result and Prognosis?
MammaPrint: Breast	RR	6; 1,913	HR: 2.84 (2.11 to 3.89) for poor prognosis vs. good prognosis	Yes
	CSS	5; 1,615	HR: 3.3 (2.22 to 4.9) for poor prognosis vs. good prognosis	Yes
	OS	1; 144	HR: 1.67 (0.73 to 3.82) for poor prognosis vs. good prognosis	No
Oncotype DX Breast	RR	6; 3,222	HR: 2.97 (2.19 to 4.02) for high risk vs. low risk	Yes
	CSS	2; 1,234	HR: 2.02 (1.35 to 3.00) for high risk vs. low risk	Yes
	OS	1; 668	HR: 1.65 (1.24 to 2.19) for high risk vs. low risk	No, single study
EGFR: Lung	RR	6; 1,870	HR: 0.87 (0.65 to 1.15); No association	No
	CSS	0; 0	NA	No
	OS	6; 1,820	HR: 0.76 (0.50 to 1.19); No association	No
KRAS: Lung	RR	4; 611	2.84 (1.14 to 7.1) *KRAS* mutation associated with greater RR	Yes
	CSS	0; 0	NA	No
	OS	2; 253	2.69 (1.91 to 3.8); 3.33 (1.03 to 10.82)	Yes[a]
BRAF: CRC	RR	5; 4,106	HR 1.07 (0.76 to 1.52) for wild-type vs. mutation	No
	CSS	7; 5,409	HR 1.50 (1.26 to 1.77) for wild-type vs. mutation	Yes
	OS	11; 7,610	HR 1.45 (1.29 to 1.62) for wild-type vs. mutation	Yes
KRAS: CRC	RR	5; 4,085	HR 1.02 (0.91 to 1.14) for wild-type vs. mutation	No
	CSS	2; 1,174	HR 1.30 (1.02 to 1.66) for wild-type vs. mutation	Yes
	OS	10; 5,328	HR 1.22 (0.93 to 1.60) for wild-type vs. mutation	No
MSI: CRC	RR	10; 7,130	HR 0.60 (0.50 to 0.72) for MSI-H vs. MSS	Yes
	CSS	6; 3,439	HR 0.65 (0.51 to 0.82) for MSI-H vs. MSS	Yes
	OS	12; 8,839	HR 0.57 (0.43 to 0.77) for MSI-H vs. MSS	Yes
Oncotype DX: CRC	RR	1; 690	HR 1.68 (1.18 to 2.38)	No, single study
	CSS	0; 0	NA	No
	OS	0; 0	NA	No
UroVysion: Bladder	RR	2; 168	Association between mutation and RR in 2 small studies	Yes, but limited to 168 subjects
	CSS	0; 0	NA	No
	OS	0; 0	NA	No

[a] Meta-analyses were conducted only when we had 3 or more HRs to combine

Notes: Table includes results of our main analyses that were based on studies rated as low or medium RoB. HRs reported are results of our meta-analyses of studies rated as low or medium RoB reporting adjusted associations for clinical validity (KQ 3).

Abbreviations: *BRAF* = gene name; CI = confidence interval; CRC = colorectal cancer; CSS = cancer-specific survival; *EGFR* = gene name; HR = hazard ratio; *KRAS* = gene name; MSI = microsatellite instability; MSI-H = microsatellite instability high; MSS = microsatellite stability: N = number; NA = not applicable; OS = overall survival; RR = risk of recurrence; vs. = versus.

Clinical Utility and the Overarching Question

Table B summarizes the evidence on the overarching question, clinical utility, and the impact of test use on treatment decisions. Ultimately, we found insufficient SOE to answer the overarching question for most tests. Even in the cases where the tests seemed to add value in determining prognosis (i.e., evidence of clinical validity), we found no evidence that using the test was related to improved outcomes for patients. For a few tests, we found low SOE, suggesting that using the test would not improve outcomes for patients—for these tests we found

evidence that did not support clinical validity (because with evidence suggesting lack of clinical validity, it is unlikely that the tests will be found to have clinical utility).

For impact on treatment decisions, we found moderate SOE that one test, Oncotype DX Breast, leads to changes in decisions. Although the decision changes were observed in both directions for individual patients, studies consistently showed an overall shift to less-intensive treatment recommendations as a result of using Oncotype DX Breast, with fewer recommendations for chemotherapy (and therefore less exposure to potential harms of chemotherapy; but studies did not follow patients to actually report on harms or to assess the overall balance of clinical benefits and harms). We found just one study of low or medium RoB for the impact of MammaPrint on treatment decisions, and we concluded that evidence was insufficient to determine the impact of MammaPrint on treatment decisions, primarily because of unknown consistency and imprecision.

Table B. Summary of findings and strength of evidence for impact on treatment decisions, clinical utility, and our overarching question

Test: Cancer	Outcome	N studies; N subjects	Conclusions	Strength of Evidence
MammaPrint: Breast	RR	6; 1,913	All studies assessed clinical validity; no evidence that test use leads to improved outcomes	Insufficient
	CSS	5; 1,615	All studies assessed clinical validity; no evidence that test use leads to improved CSS	Insufficient
	OS	1; 144	Study assessed clinical validity; no evidence that test use leads to improved mortality	Insufficient
	Decisions about Rx	1; 427	Adjuvant therapy was used less if the prognosis signature is used	Insufficient
Oncotype DX Breast	RR	6; 3,222	All studies assessed clinical validity; no evidence that test use leads to improved outcomes	Insufficient
	CSS	2; 1,234	All studies assessed clinical validity; no evidence that test use leads to improved CSS	Insufficient
	OS	1; 668	All studies assessed clinical validity; no evidence that test use leads to improved mortality	Insufficient
	Decisions about Rx	16; 2,251	~30% of treatment decisions changed by the test	Moderate
EGFR: Lung	RR	6; 1,870	All studies assessed clinical validity and found no prognostic value; test is unlikely to improve outcomes	Low
	CSS	0; 0	NA	Insufficient
	OS	6;1,820	No prognostic value; none of the reported HRs were statistically significant; test unlikely to improve mortality	Low
	Decisions about Rx	0; 0	NA	Insufficient
KRAS: Lung	RR	4; 611	All studies assessed clinical validity; no evidence that test use leads to improved outcomes	Insufficient
	CSS	0; 0	NA	Insufficient
	OS	2; 253	Studies assessed clinical validity; no prognostic value; no evidence that test use leads to improved mortality	Insufficient
	Decisions about Rx	0; 0	NA	Insufficient

Table B. Summary of findings and strength of evidence for impact on treatment decisions, clinical utility, and our overarching question (continued)

Test: Cancer	Outcome	N studies; N subjects	Conclusions	Strength of Evidence
BRAF: CRC	RR	5; 4,106	All studies assessed clinical validity; no prognostic value; test is unlikely to improve outcomes	Low
	CSS	7; 5,409	All studies assessed clinical validity; no evidence that test use leads to improved CSS	Insufficient
	OS	10; 7,610	All studies assessed clinical validity; no evidence that test use leads to improved mortality	Insufficient
	Decisions about Rx	0; 0	NA	Insufficient
KRAS: CRC	RR	5; 4,085	All studies assessed clinical validity; no prognostic value; test is unlikely to improve outcomes	Low
	CSS	2; 1,174	All studies assessed clinical validity; no evidence that test use leads to improved outcomes	Insufficient
	OS	10; 5,328	All studies assessed clinical validity; no prognostic value; test is unlikely to improve mortality	Low
	Decisions about Rx	0; 0	NA	Insufficient
MSI: CRC	RR	10; 7,130	All studies assessed clinical validity; no evidence that test use leads to improved outcomes	Insufficient
	CSS	6; 3,439	All studies assessed clinical validity; no evidence that test use leads to improved CSS	Insufficient
	OS	12; 8,839	All studies assessed clinical validity; no evidence that test use leads to improved mortality	Insufficient
	Decisions about Rx	0; 0	NA	Insufficient
Oncotype DX: CRC	RR	1; 690	Study assessed clinical validity; no evidence that test use leads to improved outcomes	Insufficient
	CSS	0; 0	NA	Insufficient
	OS	0; 0	NA	Insufficient
	Decisions about Rx	0; 0	NA	Insufficient
UroVysion: Bladder	RR	2; 168	Both studies assessed clinical validity; no evidence that test use leads to improved outcomes	Insufficient
	CSS	0; 0	NA	Insufficient
	OS	0; 0	NA	Insufficient
	Decisions about Rx	0; 0	NA	Insufficient

Abbreviations: *BRAF* = gene name; CRC = colorectal cancer; CSS = cancer-specific survival; *EGFR* = gene name; HR = hazard ratio; *KRAS* = gene name; MSI = microsatellite instability; N = number; NA = not applicable; OS = overall survival; RR = risk of recurrence; Rx = treatment.

Discussion

Our review demonstrated that the weight of published research to date in the area of molecular pathology tests for improving estimates of prognosis has focused on the clinical validity of the tests of interest in giving information about prognosis and little emphasis on how these tests can be integrated into the overall care of cancer patients in terms of measuring changes in management decisions or the effect of those altered decisions on downstream outcomes of value to patients. Such changes in management may be occurring and may be of benefit, or possibly of harm, to patients, but they have not been measured and studied, with the notable exception of the Oncotype DX assay in breast cancer, which does have a sizeable body of evidence to suggest an effect on treatment decisions (resulting in fewer recommendations for chemotherapy), though not yet a clear effect on downstream outcomes.

At this point, physicians can, in many cases, rely on the prognostic value of molecular pathology tests, share test results with patients, and discuss whether the test result indicates a better- or worse-than-average prognosis. However, in most cases, physicians cannot be sure whether using this information will improve any clinical outcomes. Although having accurate information about prognosis may be valued by patients independent of its effects on survival and recurrence outcomes, this has yet to be demonstrated for the tests of interest.

Limitations

Many of the included studies had methodological limitations, introducing some RoB. For example, most of them were observational studies assessing associations between test results and outcomes, and are susceptible to potential confounding. To limit such bias, we only included studies for KQ 3 that adjusted for most or all standard prognostic factors. Also, we assessed potential selection bias and confounding in our RoB assessments—limiting our main data syntheses to studies with low or medium RoB.

We were also not able to address the prognostic value of the tests for the Medicare population due to a lack of data that was specific to that age group. However, several studies included subjects from the Medicare agegroup and although there wre no analyses done specific to the agegroup, there was no evidence that suggested that the prognostic value of the tests would be different for this group.

Future Research

We found no direct evidence of the impact of the information provided by these tests on downstream health outcomes such as patients' quality of life or survival. Thus, future research should focus on quality of life, survival, and other health outcomes.

There is no information on the differential effects of the test by race or cancer subtype (e.g., ductal versus lobular in breast cancer) or location (e.g., proximal versus distal in CRC). As described in the results, the subpopulations that were represented in the studies varied in terms of stage, tumor type, and location in the case of CRC. Race and location have both been shown to be important predictors of the prognostic value of genetic markers in CRC.[16,17] Similar differences in prognostic value by subpopulations could be a factor in terms of *EGFR* and *KRAS* in the lung. There is thus a need to create an evidence base that replicates results in the same subpopulations, particularly in CRC and lung cancer.

As in many studies in the oncology field, the published literature uses a variety of specific definitions for outcomes such as recurrence, distant recurrence, DFS, CSS, and OS, making comparison of effects across studies more difficult. Future research should take into account careful selection of the most appropriate endpoints, both in the context of the existing body of literature and the endpoints of most clinical relevance to doctors and patients.

Conclusions

We found modest evidence supporting added prognostic value (i.e., clinical validity), beyond traditional prognostic factors, for MammaPrint; Oncotype DX Breast; *KRAS* mutation testing for lung; *BRAF* mutation testing for CRC; *KRAS* mutation testing for CRC; and MSI for CRC for RR, CSS, and/or OS. For UroVysion, which is marketed as a diagnostic (not prognostic) test, limited evidence supported an association between test result and prognosis for RR. For impact

of test use on treatment decisions, we found moderate SOE that Oncotype DX Breast leads to changes in treatment decisions, resulting in fewer recommendations for chemotherapy.

We found no studies that directly assessed the impact of test use on downstream health outcomes to establish clinical utility. Even for the tests with good evidence supporting clinical validity, we found no evidence that using the test was related to improved outcomes for patients.

Many of the included tests are currently used to predict response to specific treatments, an aspect that was not evaluated in this report. Determining whether the tests have clinical utility for predicting therapeutic response is beyond the scope of this review.

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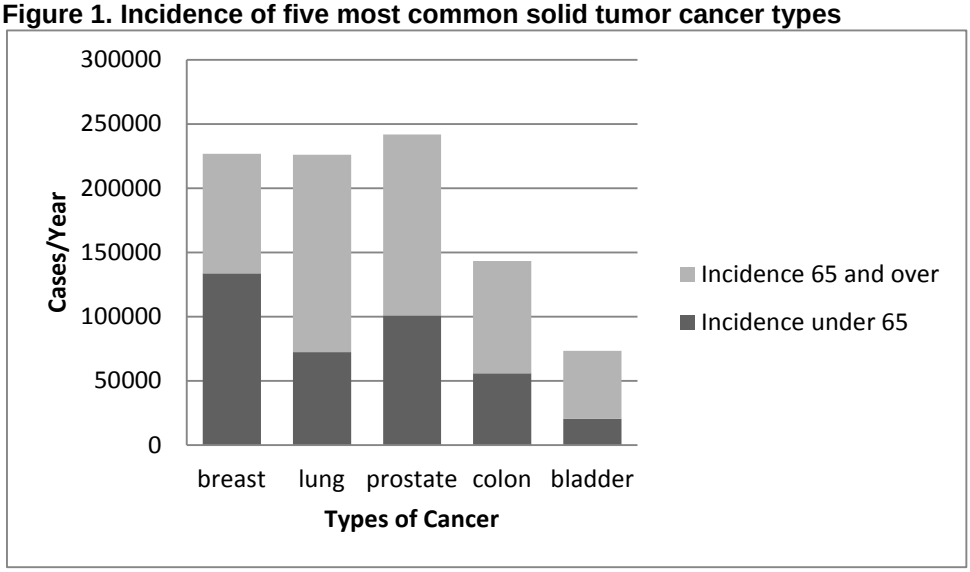
Background and Objectives

Burden of Cancer in the Medicare Population

Cancer is a leading cause of death in the United States. More than 1.6 million new cases of cancer are expected to be diagnosed in the United States in 2012.[1] Because rates of cancer incidence increase with age, almost half of these new cases will occur in the Medicare beneficiary population. As illustrated in Figure 1, adults ages 65 or older carry a disproportionate burden of new cancer diagnoses for the five most common solid tumor cancer types. For newly diagnosed Medicare beneficiaries with cancer and their care providers, estimating the prognosis of their cancer is a key step in understanding their diagnosis and forming a treatment plan. As our understanding of cancer has evolved to include the DNA mutational diversity and mRNA expression differences in the neoplastic clones, molecular pathology tests are playing an increasingly important role in determining cancer prognosis. This review aims to clarify the value of certain molecular pathology tests in determining prognosis for common cancers (breast, lung, colon, bladder) affecting Medicare beneficiaries.

Figure 1. Incidence of five most common solid tumor cancer types



Source: Data drawn from National Cancer Institute, Surveillance, Epidemiology, and End Results (SEER) Program, http://seer.cancer.gov/.[1] This figure represents an estimate of new cancer cases in the 65 or older population for the year 2012 based on overall incidence estimates for 2012 and historical distribution of new cases by age between 2005 and 2009 provided in the SEER Cancer Statistics Review.

What Is a Prognostic Test?

Prognosis is "a forecasting of the probable course and termination of an illness."[2] A prognostic test is used to predict a patient's probability of developing a disease or experiencing a medical event.[3] Determining prognosis is one of the most important steps for a newly diagnosed cancer patient and his or her health care providers. For people with cancer, a prognostic test is used to provide estimates for the likelihood of recurrence after curative-intent treatment, death from cancer, or death due to any cause after a diagnosis of cancer. In cancer research studies, these estimates are frequently referred to as recurrence-free survival, cancer-specific survival,

and overall survival. Recurrence of the cancer, cancer-specific deaths, and all-cause death are outcomes of great interest for the physician and patient as well as for researchers.

Prognostic estimates are important to cancer patients for several reasons. First, the patients and caregivers are naturally interested in finding out what to expect after the cancer is diagnosed and treated, for emotional and psychological reasons as well as for planning purposes. Second, prognostic information is often used to assist in treatment decisions, and to weigh the potential harms of treatment against the risk of disease recurrence. For example, if a patient were told that his cancer has a 10 percent chance of recurrence after initial surgical treatment, he might decide not to undergo additional chemotherapy with the potential for significant harms, whereas a patient given a 60 percent chance of recurrence might be more likely to decide to have chemotherapy. Pieces of information that distinguish patients who have different likelihoods of specific cancer outcomes are often referred to as *prognostic factors*.

Standard Prognostic Factors in Solid Tumor Cancer

The stage of a patient's cancer is one of the most powerful factors used to assess a patient's prognosis. The TNM staging system is based on the local extent of invasion by the tumor (T), whether cancer cells have spread to nearby (regional) lymph nodes (N), and whether distant (to other parts of the body) metastasis (M) has occurred.[4,5]

In addition, the grade of the tumor; other pathologic features; and other patient characteristics such as age, sex, and race are all factors that can affect prognosis depending on the primary site of the cancer. Table 1 lists the most widely accepted and validated prognostic factors for the cancer types of interest for this review.

Molecular Pathology Tests and Cancer Prognosis

As the science of cancer pathology has evolved over the past several decades, scientists have increasingly appreciated that there is biological diversity within cancers occurring in the same anatomic location and that patients with anatomically similar cancers may, in fact, have a variety of outcomes driven by molecular subtypes. The search for biomarkers to identify patients with better or worse prognoses within similar stage cancers began with the identification of distinct histologic cell types (e.g., squamous cell versus adenocarcinoma as two kinds of nonsmall cell lung cancer). These distinctions have been enriched by immunohistochemical assays, which can identify altered expression of cellular proteins. Such markers may or may not be associated with differences in prognosis. A key example includes the expression of the human epidermal growth factor 2 (HER2) receptor in breast cancer in which HER overexpression is associated with poor prognosis[6], but also serves as a predictor of response to anti-HER2 therapy. Such biomarkers have become a part of routine clinical care, and help clinicians offer more personalized prognoses and therapies to patients.

Table 1. Key standard prognostic factors in nonmetastatic solid tumors

Cancer Type	Prognostic Factor	Relationship
Colorectal	• Depth of invasion of bowel wall[a] • Invasion of adjacent structures[a] • Lymph node involvement[a] • Grade • Special cellular subtypes (e.g., mucinous, signet ring) • Lymphovascular invasion • Elevated carcinoembryonic antigen (CEA) level • Location (rectum vs. colon) • Sex • Age	Compton et al., 2000[7] Sun et al., 2009[8]
Breast	• Tumor size[a] • Tumor grade • Lymph node involvement[a] • Hormone (estrogen and progesterone) receptor status • HER2 receptor status • Inflammatory disease[a] • Age • Special cellular subtypes (e.g., mucinous, tubular)	Fitzgibbons et al., 2000[9] Rakha et al., 2008[10]
Lung	• Tumor size[a] • Invasion of adjacent tissues[a] • Spread to more than one lobe[a] • Lymph node involvement[a] • Cell type • Performance status • Weight loss • Sex	Groome et al., 2007[11] Sculier et al., 2008[12]
Bladder	• Depth of invasion of bladder wall[a] • Invasion of adjacent structures[a] • Lymph node involvement[a] • Lymphatic or vascular invasion	International Bladder Cancer Nomogram Consortium et al., 2006[13] Shariat et al., 2006[14]

[a] Factor included in American Joint Committee on Cancer staging criteria.

Abbreviations: CEA = carcinoembryonic antigen; HER2 = Human Epidermal Growth Factor Receptor 2, also known as Neu..

The search for better markers to estimate prognosis has been further enhanced with the advances in our understanding of the human genome. Genetic diversity between tumors of the same cancer type may or may not be associated with differences in prognosis. In some cases, tests for DNA mutations, DNA translocations, or mRNA expression differences (hereafter referred to as "molecular pathology tests") may offer a more accurate estimate of prognosis as an alternative or complement to traditional prognostic factors. To the extent that the results of a molecular pathology test add distinct information about a patient's likelihood of a certain outcome, such as recurrence, they can be valuable in patient education and decisionmaking.

Although molecular pathology tests are potentially valuable new tools, all such tests for common cancers are not created equal. Molecular pathology tests may vary in the extent to which they have been validated in groups of patients for whom long-term outcome data are available, and in the extent to which the patient population used in validation represents the average patient with the cancer of interest. Molecular pathology tests may also vary in their performance characteristics, including reproducibility, sensitivity and specificity, and lower limit of detection. In addition, some molecular pathology tests may change prognostic estimates by large increments when used in addition to traditional predictors, whereas others refine prognostic

estimates only slightly or not at all. All of these characteristics influence the degree to which a molecular pathology test is useful in clinical oncology practice.

How Is Prognosis Estimated?

Researchers developing prognostic models generally start with information about patient and cancer characteristics for a group of patients whose cancer outcomes (such as survival or cancer recurrence) are already known. These data are used to figure out mathematical relationships between the potential prognostic factors and the outcome of interest. Researchers must consider which outcome they wish to predict, identify the population for which they wish to make an estimate, and consider all the potential prognostic factors to include in their model based on prior literature and clinical observation.[15] Multivariable prognostic models are statistical tools that enable physicians and patients to estimate prognosis based on a combination of clinical and laboratory factors. For most cancers, the following outcomes are of greatest interest: all-cause survival (measured as time from diagnosis to death due to any cause), disease-specific survival (time from diagnosis to death due to cancer), and recurrence (time from initial surgical resection and treatment to recurrence). Thus, the mathematical models that estimate prognosis will assess the ability of the prognostic markers to predict one of these three outcomes. After comparing potential models to determine which one works best, the model's performance should be tested by using statistical methods and applying the model to different groups of patients to see if it performs as well as it did in the initial patient group. In many cases, these models can be simplified into nomograms or risk calculators that can be used in the office setting to estimate prognosis for individual patients. The usefulness of these tools depends on the validity of the predictive model that underlies them.

All prognostic estimates contain an element of uncertainty. A physician seeing a new patient may have an educated guess as to how the patient's cancer course will proceed based on the physician's experience. Although this guess may often be correct, there is still a significant degree of uncertainty. Similarly, a statistical model that estimates the likelihood of recurrence in a group of patients has some degree of uncertainty. By incorporating as many strong prognostic factors into the estimate as possible, we can reduce this uncertainty. As new candidate prognostic factors are discovered, they can be tested in combination with the known prognostic factors to investigate whether the new combination provides more accurate estimates of prognosis than the old combination (i.e., the known prognostic factors).

In evaluating prognostic tests, researchers consider *prognostic accuracy*, defined as the extent to which the test is able to predict which individuals have a higher or lower likelihood of getting the outcome (discrimination) and the extent to which the probability of a certain outcome in the population predicted by the test matches the actual probability (calibration).[16] In a disease with multiple prognostic factors, it is important to know whether a prognostic estimate incorporating a molecular pathology test of interest has improved calibration and discrimination compared with a model using only previously known prognostic factors such as those in Table 1. Further, it may be even more informative to assess net reclassification[17-19] (i.e., how much more frequently appropriate reclassification occurs than inappropriate reclassification when using a new model [incorporating a molecular pathology test] than with a model only using previously known prognostic factors). Unfortunately, not all newly discovered molecular pathology prognostic tests are evaluated in this manner. Thus, when a novel prognostic marker is reported in the scientific literature, physicians and patients may not know whether to place more value in estimates of prognosis based on older information, or on estimates based on the novel marker.

This review evaluates the value of 11 tests that are potentially useful for assessing prognosis for patients with colorectal (CRC), breast, lung, or bladder cancers. The outcome of interest in this review is recurrence of the cancer after the initial resection and treatment.

In a preliminary literature search and discussion with clinical experts for this systematic review, no commercially available molecular prognostic tests were identified for prostate cancer; therefore, prostate cancer is excluded from further consideration for this review. The molecular pathology tests of interest for the remaining four most common solid tumors among Medicare beneficiaries (Table 2) were selected based on preliminary literature searches, consultation with clinical experts, and consultation with the funding agency.

Table 2. Descriptions of genomic tests evaluated in this report

Cancer Type	Vendor	Vendor Test, Kit, or LDT	FDA-Approved	Sample Requirements	Type of Analyte	Panel Size	Neoplasms to be Tested	Results Reported from Which Lab?
Colorectal ACa								
MSI	Promega	Kit	No	Ca and NL FFPE tissue	DNA	5 microsatellites	Colorectal ACa	MGP
MLH-1 PHM	Qiagen	Kit (Pyro seq)	No	FFPE tissue	DNA	1 locus	Colorectal ACa	MGP
BRAF mutation	(1) Qiagen (2) Roche	(1) Kit (Pyro seq) (2) Quant PCR	(1) No (2) Yes	FFPE tissue	DNA	1 locus	Colorectal ACa	MGP
KRAS mutation	Qiagen	Kit (Pyro seq)	No	FFPE tissue	DNA	1 locus	Colorectal ACa	MGP
Oncotype DX	Genomic Health	Vendor IVDMIA	No	FFPE tissue	mRNA	12 loci	Stg II CRC ACa	Vendor
Breast Ca								
Oncotype DX	Genomic Health	Vendor IVDMIA	No	FFPE tissue	mRNA	21 loci	ER+ LN− BrCa	Vendor
MammaPrint	Agendia	Vendor IVDMIA	Yes	Frozen or FFPE tissue	mRNA	70 loci	<5 cm LN− BrCa	Vendor
Lung Ca, NSCLC								
ALK transloc'n	Vysis	Kit	Yes	FFPE tissue	DNA (interphase chromosomes)	1 locus	NSCLC	Cytogenetics
EGFR mutation	(1) Illumina	(1) TruSeq Amplicon Cancer Panel	No	FFPE tissue	DNA	1 locus	NSCLC	(1) MGP
	(2) Ion Torrent	(2) Ion AmpliSeq Cancer Panel	No	FFPE tissue	DNA	1 locus	NSCLC	(2) MGP
	(3) Qiagen	(3) Kit (Pyro seq) Quant PCR	Yes	FFPE tissue	DNA	1 locus	NSCLC	(3) MGP
	(4) Integrated Onc/Lab Corp	(4) Ref lab Sanger sequencing	No	FFPE tissue	DNA	1 locus	NSCLC	(4) Vendor
	(5) Roche	(5) Cobas Real-time PCR	No	FFPE tissue	DNA	1 locus	NSCLC	(5) MGP
KRAS mutation	Qiagen	Kit (Pyro seq)	No	FFPE tissue	DNA	1 locus	NSCLC	MGP

Table 2. Descriptions of genomic tests evaluated in this report (continued)

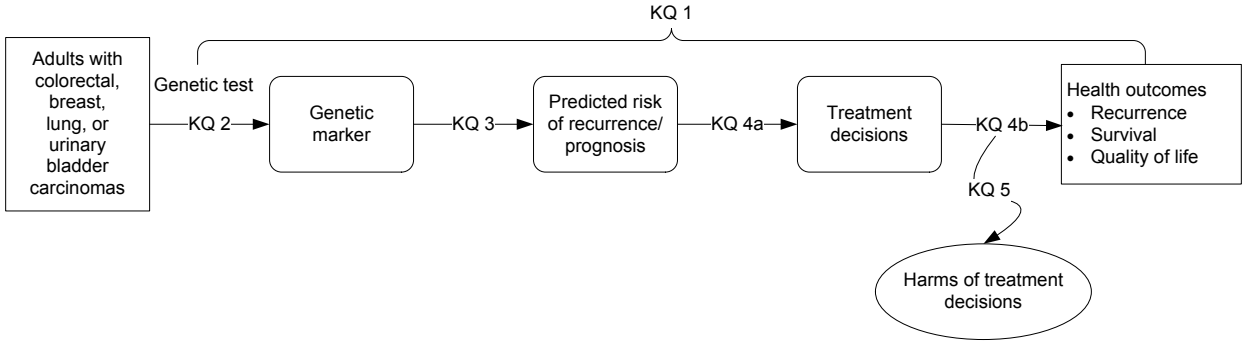
Cancer Type	Vendor	Vendor Test, Kit, or LDT	FDA-Approved	Sample Require-ments	Type of Analyte	Panel Size	Neo-plasms to be Tested	Results Reported from Which Lab?
Bladder (Urothe-lial) Ca								
UroVysion	Vysis	Kit	Yes	Alcohol-fixed	Cells	DNA (4 inter-phase chromo-somes)	Urothelial	Vendor

Abbreviations: ACa = adenocarcinoma; *ALK* = gene name; *BRAF* = gene name; Ca = cancer; BrCa = breast cancer; CRC = colorectal cancer; DNA = deoxyribonucleic acid; DX = diagnosis; *EGFR* = gene name; ER+ = estrogen receptor positive; FDA = Food and Drug Administration; FFPE = formalin-fixed paraffin-embedded tissue; IVDMIA = in vitro diagnostic multivariate index assays; *KRAS* = gene name; LDT = lab-developed test; LN- = lymph node; MGP = molecular genetic pathology; MLH-1 PHM = MLH-1 gene name promoter hypermethylation; mRNA = messenger ribonucleic acid; MSI = microsatellite instability; NL = normal; NSCLC = nonsmall cell lung carcinoma; PCR = polymerase chain reaction; seq = sequence; Stg = stage.

Scope and Objectives of the Review

These genetic tests are used in two different contexts. In one, the tests are used in a specific context of a diagnostic/therapy combination, where the diagnostic test is being used to predict response to a very specific treatment. In the second context, the genetic tests are used to estimate the patient's prognosis, and physicians use this prognostic information to choose from a variety of different treatment options. CMS requested this report to evaluate the second context. Therefore, studies that evaluate specific diagnostic/therapy combinations are excluded from this reporte thus did not include studies that were assessing tests for that purpose.The main purpose of this review is to determine whether the tests improve estimation of prognosis (for recurrence); affect physician decision-making; and thereby improve outcomes for patients with colorectal, breast, lung, or bladder cancer compared with traditional assessment of prognosis of recurrence. This technology assessment will use the analytic framework illustrated in Figure 2 and the associated Key Questions (KQs) to systematically review the evidence on 11 molecular pathology tests. In this review, we address the KQs listed below.

Figure 2. Analytic framework



Abbreviation: KQ = Key Question.

The following tests are under consideration for this assessment and apply to all KQs: microsatellite instability for CRC, MLH1 promoter methylation for CRC, *KRAS* mutation testing for CRC, *BRAF* mutation testing for CRC, Oncotype DX Colon for CRC, Oncotype DX Breast

for breast cancer, MammaPrint for breast cancer, *ALK* translocations for non-small cell lung carcinoma (NSCLC), *EGFR* for NSCLC, *KRAS* for NSCLC, and UroVysion for urinary bladder cancer.

KQ 1. Overarching Question: Is there direct evidence that the addition of the specified molecular pathology tests used alone or in combination with traditional prognostic factors changes physician decisionmaking and improves outcomes for adult patients with CRC, breast, lung, or bladder cancer compared with the use of traditional factors to predict risk of recurrence (RR) for adults with these cancers?

KQ 2. Analytic Validity: Does existing evidence establish the technical accuracy and reliability of these tests for detecting the relevant molecular analytes?

KQ 3. Clinical Validity: Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4. Clinical Utility: Does existing evidence support clinical utility of the molecular pathology tests?

KQ 4a. What is the evidence that the prognostic information provided by the molecular pathology tests modifies physician decisions regarding use of adjuvant antineoplastic chemo- and/or radiotherapy, enhanced diagnostic testing for recurrence, and/or surgery among adult patients with malignant tumors?

KQ 4b. What is the evidence that modified decisions lead to improved outcomes, including patient-centered outcomes such as improved quality of life, reduced disease recurrence, increased overall survival (OS) or disease-free survival (DFS), or reduced therapeutic side effects?

KQ 5. What are the harms associated with treatment decisions that are informed by the molecular pathology tests?

Methods

The methods for this systematic review follow the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Medical Test Reviews*.[3,20-23]

Literature Search Strategy

Search Strategy

To identify articles relevant to each Key Question (KQ), we searched PubMed®, the Cochrane Library, and EMBASE®. The full search strategy is presented in Appendix A. We used either Medical Subject Headings (MeSH) or major headings as search terms when available or key words when appropriate, focusing on terms to describe the relevant cancers and tests of interest. Searches were run by an experienced information scientist serving as the Evidence-based Practice Center (EPC) librarian and were peer reviewed by another information scientist.

We limited the electronic searches to English-language, adult, and human-only studies. Sources were searched from inception through November 2013. We manually searched reference lists of pertinent review articles and studies meeting our inclusion criteria to look for any relevant citations that our searches might have missed. We imported all citations into an EndNote® X5 (Thomson Reuters, New York, NY) electronic database.

We also searched for unpublished studies relevant to this review using test developers' Web sites, ClinicalTrials.gov, the Food and Drug Administration (FDA) Web site, Health Services Research Projects in Progress, and the European Union Clinical Trials Register. In addition, we requested unpublished information from the College of American Pathologists (CAP) and from the relevant companies, asking for data that they believe should be considered for the review. In cases in which relevant information was unclear or not reported, we contacted authors to get additional or unpublished information.

Any literature suggested by reviewers was investigated and, if appropriate, incorporated into the final review. We determined appropriateness for inclusion in the review by the same methods described in this chapter.

Eligibility Criteria

We developed eligibility (inclusion and exclusion) criteria for Populations, Interventions (i.e., tests for this report), Comparators, Outcomes, Timing, Settings (PICOTS), and study designs (Table 3). We included studies meeting the criteria described in Table 3 that were relevant to at least one of the KQs.

Table 3. Inclusion/exclusion criteria

Category	Inclusion	Exclusion
Population	Adult patients (19 years of age or older) with cancer of the colon/rectum, breast, lung, or urinary bladder (cancer types known to be of higher incidence in the core Medicare beneficiary population [people 65 years of age or older])	People 18 years of age or younger; all other tumor types and sites. Studies focused on a population with advanced/metastatic cancer.
Interventions (i.e., tests)	The following molecular pathology tests when used alone or in combination with "traditional" prognostic factors to measure the likelihood of malignant tumor recurrence (e.g., tumor size, tumor grade, estrogen receptor status; see Table 1): Lung cancer: *ALK*, *EGFR*, *KRAS* CRC: Microsatellite instability (MSI), MLH1 promoter methylation, *KRAS*, *BRAF*, Oncotype DX Colon Breast cancer: Oncotype DX Breast, MammaPrint Urinary bladder cancer: UroVysion	Molecular pathology tests used to measure the likelihood of malignant tumor recurrence that are not commercially available in the United States. Studies focused on predicting response to treatments (e.g., studies focused on response to gefitinib for people with advanced lung cancer).
Comparators	We will compare the molecular pathology tests listed above with standard tests or markers (see Introduction) used to measure the likelihood of malignant tumor recurrence. We will collect information about comparators as they are defined and reported in each study. For KQs 1, 4, and 5, we are looking for studies that compare an eligible molecular pathology test plus all known prognostic factors with all known prognostic factors alone to isolate whether the test adds any value (benefit) or introduces additional harms (KQ 5). Alternatively, studies that compare an eligible molecular pathology test alone with known prognostic factors are also eligible for inclusion. If a study uses most of the known prognostic factors but not all of them, it could also meet our inclusion criteria, and the comparison would be considered in the risk of bias (RoB) assessment (related mainly to confounding and approach to statistical adjustment). For KQ 2 (analytic validity), comparators also include intra- and interlaboratory repeat testing of samples. For KQ 3 (clinical validity), cohort studies that do the test on everyone, follow them over some period of time to capture relevant outcomes, and then do a multivariate analysis to adjust for known factors and to determine whether the tests have prognostic value for predicting recurrence are eligible. Such studies must compare those with different test results (e.g., those with a mutation versus those who are wild-type) to establish prognostic value, adjusted for known factors. To inform whether molecular pathology tests add value above standard prognostic factors, results must be adjusted for known prognostic factors (or they must be addressed in other ways, such as through inclusion/exclusion criteria of the study or stratification). Relevant case-control studies for KQ 3 could compare cases (people with recurrence) and controls (without recurrence) by rates of exposure (e.g., test positive vs. test negative), adjusting for known prognostic factors.	Unadjusted studies demonstrating associations between test results (e.g., those with a mutation versus those who are wild-type) and outcomes.

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Table 3. Inclusion/exclusion criteria (continued)

Category	Inclusion	Exclusion
Outcomes	KQ 1. Overarching question. Studies must provide direct evidence of the impact of a test of interest on physician decision-making (regarding the use of adjuvant anti-neoplastic chemo- and/or radiotherapy, enhanced diagnostic testing for recurrence, or preventive surgery) and also on health outcomes (overall survival, disease-free survival, time to recurrence, or quality of life). KQ 2. Analytic validity Tissue sample acceptance/rejection criteria. Sensitivity/specificity of testing for each marker at assay conditions. Degree of variation in the results if the same tumor is tested in multiple laboratories. Uniqueness of the markers used in the panel and their robustness to contamination. Quality control standards for considering the validity of the overall assay (for multiplex tests). Proportion of probes or antibodies that must return a valid result (for multiplex tests). KQ 3. Clinical validity Prognostic value for recurrence (e.g., time to recurrence and disease-free survival) and overall survival. Differences in prognostic value associated with patient characteristics. Differences in prognostic value between non-Medicare and Medicare population. KQ 4. Clinical utility 4a. Decision-making Modification of physician decisions regarding the use of the following: adjuvant anti-neoplastic chemo- and/or radiotherapy enhanced diagnostic testing for recurrence preventive surgery 4b. Health outcomes Overall survival, disease-free survival, time to recurrence, quality of life (must be assessed using a valid and reliable quality-of-life measurement tool) KQ 5. Harms Adverse effects of tests, adverse effects of adjuvant therapy, decreased quality of life	Prediction of response to treatment. Progression-free survival is not an eligible outcome.
Time Frame/ Duration	We will include studies of any duration that otherwise meet inclusion criteria.	

Table 3. Inclusion/exclusion criteria (continued)

Category	Inclusion	Exclusion
Study Designs	Include/eligible study designs, by KQ: KQ 1a. Randomized controlled trials (RCTs), non-RCTs, prospective cohort studies with eligible comparison groups, and case-control studies that directly assess the impact of a test of interest on physician decision-making (regarding the use of adjuvant antineoplastic chemo- and/or radiotherapy, enhanced diagnostic testing for recurrence, or preventive surgery) and also on health outcomes (overall survival, disease-free survival, time to recurrence, or quality of life). KQ 2. Collaborative studies using panels (ideally large panels) of well-characterized samples, data from external proficiency testing schemes, data from inter-laboratory comparison programs, test and retest of samples, or validation studies (including those from manufacturers). KQ 3. Prospective and retrospective cohort studies and case-control studies with eligible comparison groups. This could also include publications of validated clinical decision algorithms that were developed using cohort data to quantify the contributions of different variables (e.g., molecular pathology test result, tumor size, tumor grade) in order to determine classification/interpretation of a molecular pathology test result for prognosis. KQ 4a. RCTs, non-RCTs, prospective and retrospective cohort studies with eligible comparison groups, and case-control studies. Case series will be considered for KQ 4a for decision-making outcomes only if other eligible study designs are not available. KQ 4b.[a] RCTs, non-RCTs, prospective and retrospective cohort studies with eligible comparison groups, and case-control studies. KQ 5. RCTs, non-RCTs, prospective and retrospective cohort studies with eligible comparison groups, and case-control studies.	Non-English publications, systematic and nonsystematic reviews, case series (except as noted for KQ 4a; we determined that the RoB in case series is too high to provide valid and reliable information for the other KQs), letters, editorials, abstracts, and observational studies without comparison groups.
Settings	Any country (no limits)	

[a] An RCT that randomized subjects to use a molecular pathology testmolecular pathology test alone or in combination with standard prognostic factors compared with standard prognostic factors alone to inform decisions and that reported health outcomes would address the overarching question (KQ 1), whereas KQ 4b would include studies that evaluated the link between decisions and health outcomes.

Abbreviations: *ALK* = gene name; *BRAF* = gene name; DX = diagnosis; *EGFR* = gene name; KQ = Key Question; *KRAS* = gene name; MLH-1 = gene name promoter hypermethylation; MSI = microsatellite instability; RCT = randomized controlled trial; RoB = risk of bias.

Study Selection

We developed and pilot tested review forms for review of titles/abstracts and full texts. All references were tracked in a Microsoft Excel® Version 14.0 (Microsoft Corporation, Redmond, WA) database. Two trained members of the research team independently reviewed each title and abstract identified through searches for eligibility. Studies marked for possible inclusion by either reviewer underwent a full-text review. For studies that lacked adequate information to determine inclusion or exclusion, we retrieved the full text and then made the determination. If the necessary information in full-text articles was unclear or missing, we contacted authors of the publications.

Two trained members of the research team independently reviewed each full-text article for inclusion or exclusion based on the eligibility criteria described above. If both reviewers agreed that a study did not meet the eligibility criteria, we excluded it. If the reviewers disagreed, they resolved conflicts by discussion and consensus or by consulting a third member of the review

team. We recorded the principal reason that each excluded full-text publication did not satisfy the eligibility criteria (Appendix B).

Data Extraction

For studies that met our inclusion criteria, we extracted study characteristics and results into evidence tables. We designed, pilot tested, and used structured data extraction forms to gather pertinent information from each article; this included characteristics of study populations, settings, interventions, comparators, study designs, methods, and results. Trained reviewers extracted the relevant data from each included article into the data extraction forms. All data extractions were reviewed for completeness and accuracy by a second member of the team. All data extraction was performed using Microsoft Excel® software.

Risk-of-Bias Assessment of Individual Studies

We assessed the RoB (internal validity) in the reviewed studies using an approach supported by the *Methods Guide for Medical Test Reviews*.[3] For studies of analytic validity, we considered the potential for bias due to flaws in the sample selection, testing protocol, reference standards, verification procedures, interpretation, and/or analysis. We used the questions relevant for prognostic tests from the QUADAS-2[24,25] (which was developed for diagnostic tests) for assessing risk of relevant biases. For studies of clinical validity and clinical utility, we assessed the potential for selection bias, confounding, performance bias, attrition bias, and detection bias. We assessed these biases using relevant questions and predefined criteria based on guidance from the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* and the RTI Question Bank.[26]

We summarized RoB for each study as low, medium, high, or unclear. In general, studies with a low RoB are those that have a low risk of selection bias, use valid and reliable outcome measures, use appropriate statistical and analytical methods, have low attrition, and report methods and outcomes clearly and precisely. Studies with a medium RoB are those that do not meet all criteria required for low RoB but do not have flaws that are likely to cause major bias. Missing information often led to ratings of medium as opposed to low RoB. Studies with inadequate reporting to allow assessment of RoB were described as having unclear RoB—this was often the case for abstracts from conference proceedings. Studies with a high RoB are those with at least one substantial flaw in the study's design, conduct, or analysis that could invalidate the results. Two independent reviewers assessed the RoB for each study. Disagreements were resolved by discussion and consensus or by consulting a third member of the team. Appendix C details the criteria used for evaluating the RoB of all included studies and explains the rationale for high RoB ratings.

Data Synthesis

For clinical validity, data were synthesized for each test by cancer type using meta-analytic techniques described in Hedges & Vevea.[27] The measure of the effect size in most studies was a hazard ratio (HR). A few studies had odds ratios. A summary HR was estimated for any outcome that had three or more independent HR estimates. In cases where subpopulations from one study were included in the sample for another study, we used the study with the largest included population in our meta-analyses (to avoid double-counting any data). If studies provided separate estimates for different subsamples (e.g., node negative and node positive), both estimates were

included if no overall HR was provided. If an overall HR for the entire sample and the separate HRs for subsamples were provided, then only the overall measure was used.

If the test is non-informative, we expect that the probability of experiencing the end point would be the same for either group, with an HR of 1. If the HR is greater than 1, the probability of the endpoint is higher in the group with the higher hazard. If the HR is lower than 1, the probability of experiencing the endpoint is lower in the group with the lower hazard. For example, an HR of 2 for CSS indicates that one group (e.g., those with high risk results for Oncotype DX Breast) has twice the rate per unit of time as the comparison group (e.g., those with low-risk test results).

The standard error (SE) of the HR was used to estimate the variance of the effect size. In most cases, the SE was estimated from the 95% confidence interval (CI). We tested the null hypothesis of homogeneity of effect sizes across the studies[27,28] for each of the outcomes. If the null hypothesis was rejected at a significance level of 0.05, the summary HR was estimated using a random effects model; if not, it was estimated using a fixed effects model. In both cases, the inverse of the variance was used to estimate a weighted summary HR. Forest plots with indicators of the weight assigned to each study were used to help visualize the contributions of each study and to show the summary HR.

We did not include studies with a high or unclear RoB in our main analyses/main data syntheses.

Strength of the Body of Evidence

We graded the strength of evidence (SOE) based on the guidance established for the Evidence-based Practice Center program Program.[29,30] Developed to grade the overall strength of a body of evidence, this approach incorporates four key domains: RoB (includes study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, strength of association (magnitude of effect), and publication bias. Table 4 defines the grades of evidence that we assigned.

Table 4. Definitions of the grades of overall strength of evidence

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

Source: Owens et al., 2010[29]

For each test being evaluated in this review, two reviewers assessed each domain for each key outcome and determined an overall SOE grade based on domain ratings. In the event of disagreements on the domain or overall grade, they resolved differences by consensus discussion or by consulting with a third investigator.

We attempted to find studies that directly address the overarching question (KQ 1). If we did not find adequate direct evidence addressing the overarching question, we attempted to construct an indirect chain of evidence (using studies identified for the other KQs).

Appendix D includes tables showing our assessments for each domain and resulting SOE grades for each outcome, organized by type of cancer and test. We graded the SOE separately for analytic validity and for evidence on our overarching KQ. For analytic validity, we graded the SOE for the following: sensitivity and specificity, positive and negative predictive value, and cross-lab validity. For evidence on the overarching KQ, we graded the SOE for the following outcomes: risk of recurrence, cancer-specific survival, overall survival, and decisions about treatment.

Applicability

We assessed applicability of the evidence following guidance from the *Methods Guide for Comparative Effectiveness Reviews*.[28,31] We used the PICOTS framework to explore factors that affect applicability. Some factors identified that may limit the applicability of evidence include age, sex, and race or ethnicity of enrolled populations.

Peer Review and Public Commentary

Peer Review

The comments were generally favorable from the peer reviewers. Two main areas were identified as needing revisions.

1. Emphasizing that this report focused on the prognostic value of the tests and did not examine the predictive value of the tests (i.e., in predicting response to treatment).
2. Incorporating CAP's information into the description of the analytic validity for the tests and general comments on improving the description of analytic validity of the tests.

We have incorporated these suggestions in the document.

Public Comments

A lot of the public comments were from the manufacturers of the tests examined. Besides disputing some of the SOE grades and conclusions or suggesting revisions to KQs, one salient issue raised by a manufacturer was about including UroVysion in the report. Abbott Molecular pointed out that UroVysion was not designed or marketed as a test to assess prognosis and requested that the test be excluded from the report.

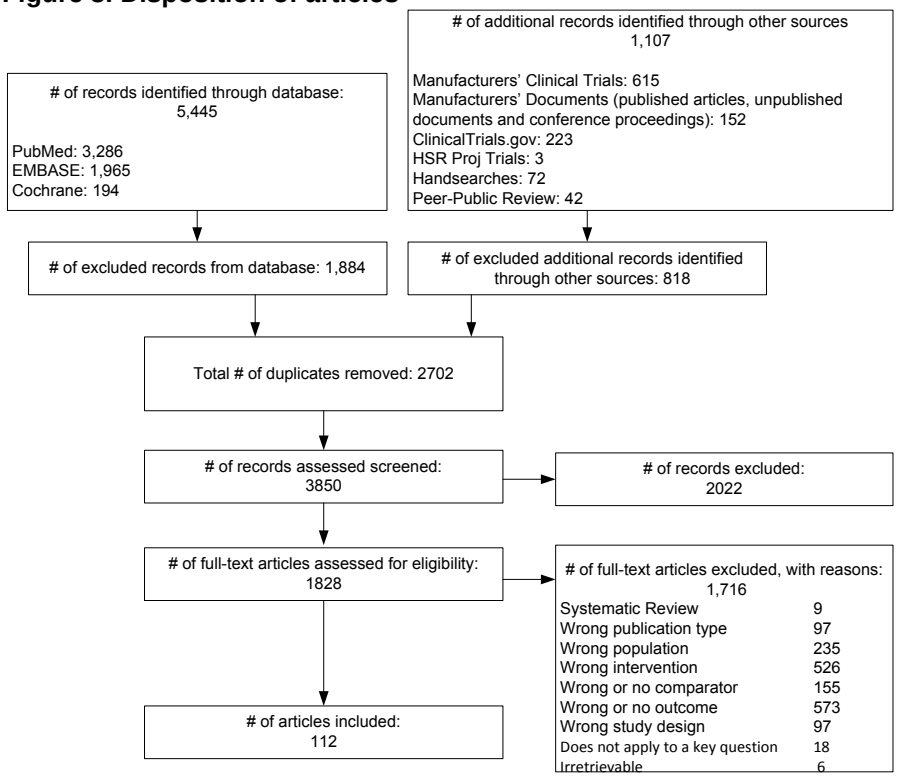
We have decided to keep UroVysion in the report but have added clear statements in various sections to clarify the intended use of the test.

Results

Literature Search

We included 112 publications reporting on the tests of interest (Figure 3). We included 21 publications for Key Question (KQ) 2, 70 for KQ 3, and 22 for KQ 4a. We found no eligible studies for KQ 1, KQ 4b, or KQ 5. Of the included studies, we rated 31 as low, 57 as medium, 12 as high, and 12 as unclear risk of bias (RoB).

Figure 3. Disposition of articles



Results of Included Studies

Key Question 1. Direct Evidence That Using the Tests Changes Physician Decisionmaking and Improves Outcomes

We found no eligible studies that addressed this overarching question.

Key Question 2. Analytic Validity

We included 21 studies, using a total of 23 different tests (Table 5) as well as data from the College of American Pathologists. We analyzed marker test performance and intra/interlab reproducibility.

Table 5. Characteristics of included studies reporting on analytic validity, by test and cancer

Author, Year, Design, Test (Primary Site), Risk of Bias	Vendor, Developer of Test	Tissue Sample Requirements, Type of Analyte, Measure Technique	Neoplasms, Lab Reporting Results, Test Measure, Tissues in Sample
Abbot Labs, 2011[32] Validation *ALK* (lung) Unclear	Abbot Labs Vendor	FFPE DNA fluorescence in situ hybridization (FISH)	Nonsmall cell lung cancer Authors' lab(s) Chromosome rearrangements 136
Angulo, 2013[33] Test-retest *EGFR* (lung) Low	Qiagen Vendor	FFPE DNA PCR followed by *therascreen*® *EGFR* Mutation Kit	Nonsmall cell lung cancer Histology: Carcinomas NOS (23.5%) Squamous cell carcinomas (10.3%) Adenocarcinomas (64%) Large cell carcinomas (2.2%) Authors' lab(s) *EGFR* mutations at exons 19 to 21 136
Bando, 2010[34] Validation *KRAS* (colorectal) Medium	DxS Ltd.; Vienna Lab Diagnostics, Vendor	FFPE DNA Direct (Sanger) sequencing; *therascreen KRAS* Mutation Kit: Allele-specific PCR with Scorpion fluorescent probes (ARMS/S); *KRAS* Strip-Assay: Reverse hybridization (RH)	CRC Authors' lab(s) *KRAS* mutations at codons 12 and 13 100
Beau-Faller, 2011[35] Validation *EGFR* (lung) Low	NA Lab developed for each center	FFPE and frozen DNA Direct or nested sequencing; each center used their own standard procedure.	Nonsmall cell lung cancer NR *EGFR* mutations at exons 18 to 21 74
Beau-Faller, 2009[36] Test-retest *KRAS* (lung) Low	Roche (Germany), Eurogentec (Belgium), Timolbiol (Germany); Lab developed	Frozen DNA PNA-mediated PCR clamping	Nonsmall cell lung cancer Authors' lab(s) *KRAS* mutations at codons 12 and 13 114
Beau-Faller, 2011[35] Validation *KRAS* (lung) Low	NA Lab developed for each center	FFPE and frozen DNA Direct or nested sequencing; each center used their own standard procedure.	Nonsmall cell lung cancer NR *KRAS* mutations at exon 2 74

Table 5. Characteristics of included studies reporting on analytic validity, by test and cancer (continued)

Author, Year, Design, Test (Primary Site), Risk of Bias	Vendor, Developer of Test	Tissue Sample Requirements, Type of Analyte, Measure Technique	Neoplasms, Lab Reporting Results, Test Measure, Tissues in Sample
Clark-Langone 2010[37] Test-retest Oncotype DX (colorectal) Medium	Genomic Health Vendor	FFPE RNA RT-PCR of 12-gene Recurrence Score Assay	Stage II adenocarcinoma and mucinous carcinoma Authors' lab(s) Expression levels NR
Cronin, 2007[38] Test-retest Oncotype Dx (Breast) Unclear	Genomic Health Vendor	FFPE RNA RT-PCR of 21-gene Recurrence Score Assay	Node-negative, estrogen receptor–positive breast cancer Vendor's lab Expression levels NR
Delahaye, 2013[39] Test-retest MammaPrint (breast) Medium	Agendia NV, Amsterdam, The Netherlands Vendor	Fresh tissue RNA Microarray	Early-stage, invasive breast cancer Vendor's labs Expression levels N = 100 (cross lab validity tests)
Feigelson, 2012[40] KRAS (colorectal) Low	NA Lab developed for each center	FFPE DNA PCR amplification followed by Direct Sanger sequencing, PCR amplification followed by standard bidirectional sequencing, PCR amplification followed by sequencing, Single nucleotide primer extension with fragment analysis by capillary electrophoresis using a modified SNaPshot assay, or Qualitative real time PCR.	CRC (18 adenocarcinoma, 2 carcinoma) Genzyme, Clarient, Quest Diagnostics, Henry Ford Health System & Molecular and Medical Genetics-Oregon Health and Science University KRAS mutations at codons 12 and 13 20
Gao, 2010[41] Validation *KRAS* (colorectal) Unclear	Vienna Lab of Austria CND	FFPE DNA Dideoxy sequencing, *KRAS* StripAssay and pyrosequencing	CRC Authors' lab(s) *KRAS* mutation s at exon 2 NR

Table 5. Characteristics of included studies reporting on analytic validity, by test and cancer (continued)

Author, Year, Design, Test (Primary Site), Risk of Bias	Vendor, Developer of Test	Tissue Sample Requirements, Type of Analyte, Measure Technique	Neoplasms, Lab Reporting Results, Test Measure, Tissues in Sample
Gonzalez de Castro 2012[42] Test-retest *KRAS* (colorectal) Low	Roche Molecular Systems, Inc., Qiagen Vendor	FFPE DNA Cobas *EGFR* Mutation Test (AS-PCR) *therascreen EGFR*29 Mutation Kit (ARMS); 2× bidirectional; Sanger sequencing	CRC 2 clinical site labs *KRAS* mutations at codons 12 and 13 115
Hancer, 2011[43] Cohort *KRAS* (colorectal) Unclear	1) Big Dye Terminator kit v.3.1 (Applied Biosystems, Foster City, CA); 2) DxS Ltd., Manchester, United Kingdom; 3) Entrogen, Tarzana, CA Vendor	FFPE DNA Dideoxy sequencing, *therascreen KRAS* kit, and Entrogen *KRAS* mutation analysis kit	Adenocarcinomas of the colon and the rectum Authors' lab(s) *KRAS* mutations at codons 12 and 13 64
Jancik, 2012[44] Test-retest *KRAS* (lung) High	PyroMark KRAS assay test: Biotage, Uppsala, Sweden *therascreen* DxS *KRAS* Mutation Kits KR-21 and KR-22: QiaGen, Hilden, Germany KRAS StripAssay REF 5–590: ViennaLab Diagnostics GmbH, Vienna, Austria Direct sequencing and HRM analysis used components from various vendors Vendor	Frozen DNA Direct sequencing, Pyrosequencing, *therascreen* DxS, KRAS StripAssay kits, and HRM analysis	Nonsmall cell lung cancer Authors' lab(s) *KRAS* mutations at codons 12 and 13 131
Kobunai, 2010[45] Test-retest *KRAS* (colorectal) Low	Qiagen, Panagene Lab developed	Frozen DNA Peptide nucleic acid (PNA)-clamp real-time PCR	CRC Authors' lab(s) *KRAS* mutations at codons 12 and 13 224

Table 5. Characteristics of included studies reporting on analytic validity, by test and cancer (continued)

Author, Year, Design, Test (Primary Site), Risk of Bias	Vendor, Developer of Test	Tissue Sample Requirements, Type of Analyte, Measure Technique	Neoplasms, Lab Reporting Results, Test Measure, Tissues in Sample
Lopez-Rios 2013[46] Test-retest *EGFR* (lung) Low	Roche Molecular Systems, Inc., Qiagen, Vendor	FFPE DNA Cobas *EGFR* Mutation Test (AS-PCR) *therascreen EGFR*29 Mutation Kit (ARMS); 2× bidirectional; Sanger sequencing	Nonsmall cell lung cancer 2 clinical site labs *EGFR* mutations at exons 18 to 21 124
Mancini, 2010[47] Test-retest *BRAF* (colorectal) Medium	NA Lab developed	Frozen DNA PCR: Cold PCR—sensitivity then evaluated by high-resolution melting (HRM) analysis and sequencing	Sporadic colorectal cancer (CRC) Authors' lab(s) *BRAF* mutations at exon 15 117
Mancini, 2010[47] Test-retest *KRAS* (colorectal) Medium	NA Lab developed	Frozen DNA PCR: Cold PCR—sensitivity then evaluated by HRM analysis and sequencing	Sporadic CRC Authors' lab(s) *KRAS* mutations at codons 12 and 13 117
Naoki, 2011[33] Test-retest EGRF (lung) Low	NA Lab developed	FFPE and frozen DNA PCR: PCR-invader method	Nonsmall cell lung cancer BML *EGFR* mutations at exons 18 to 21 54
Pang, 2011[48] Validation *KRAS* (colorectal) High	Qiagen Vendor	FFPE DNA PCR amplification	Stage IV colorectal adenocarcinoma Authors' lab(s) *KRAS* mutations at exons 2 and 3 11
Pang, 2011[48] Validation *BRAF* (colorectal) High	Qiagen Vendor	FFPE DNA PCR amplification	Stage IV colorectal adenocarcinoma Authors' lab(s) *BRAF* mutations at exon 15 11

Table 5. Characteristics of included studies reporting on analytic validity, by test and cancer (continued)

Author, Year, Design, Test (Primary Site), Risk of Bias	Vendor, Developer of Test	Tissue Sample Requirements, Type of Analyte, Measure Technique	Neoplasms, Lab Reporting Results, Test Measure, Tissues in Sample
Poulet, 2012[47] Test-retest MammaPrint (breast) Unclear	NR NR	Frozen DNA Microarray	ER+, HER2-neg early breast cancer Authors' lab(s) Cluster analysis 67
Poulet, 2012[47] Test-retest Oncotype DX (breast) Unclear	NR NR	Frozen RNA RT-PCR of 12-gene Recurrence Score Assay	ER+, HER2-neg early breast cancer Authors' lab(s) Expression levels 67
Sriram, 2011[33] Cohort *EGFR* (lung) Low	NA Lab developed	Frozen DNA ME-PCR; HRM	Nonsmall cell lung cancer NR *EGFR* mutations(exon 19 deletion and exon 21 L858R) 522 tumor tissue and 64 matched serum samples
Van't Veer, 2002[49] Validation MammaPrint (breast) Medium	NA Lab developed	Frozen DNA Microarray	Breast cancer Authors' lab(s) Cluster analysis 78 in development set, 19 in validation set

Abbreviations: ARMS = Amplification Refractory Mutation System; ARMS/S = Amplification Refractory Mutation System and a Scorpion fluorescent primer/probe system; BML = Bio Medical Laboratories (Tokyo, Japan); *BRAF* = v-Raf murine sarcoma viral oncogene homolog B1; DNA = deoxyribonucleic acid; *EGFR* = epidermal growth factor receptor gene; FFPE = formalin-fixed, paraffin-embedded; HRM = high-resolution melting; *KRAS* = V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; ME = mutant enriched; NA = not applicable; NOS = not otherwise specified; NR = not reported; PCR = polymerase chain reaction; PNA = peptide nucleic acid; RH = reverse hybridization.

Of the 11 potentially considered molecular pathology tests of interest, we found published studies rated as low or medium RoB for 6 tests: MammaPrint mRNA expression for breast cancer, *EGFR* mutations and *KRAS* mutations for lung cancer, *KRAS* mutations and *BRAF* mutations for colorectal cancer (CRC), and Oncotype DX Colon mRNA expression for CRC. The published studies that we identified reporting on *ALK* cytogenetics for lung cancer, Oncotype DX Breast mRNA expression for breast cancer, and MLH1 promoter methylation for CRC were rated as high or unclear RoB. Results of the included studies are provided in Table 6.

Table 6. Results of included studies reporting on analytic validity, by test and cancer

Author, Year, Design, Test (Primary Site), Risk of Bias	Tissue Sample Requirements, Type of Analyte, Measure Technique	Neoplasms, Lab Reporting Results, Test Measure, Sample Size	Marker Sensitivity	Marker Specificity	Cross-Lab Validity Checked, Degree of Cross-Lab Variation
Abbot Labs, 2011[32] Validation *ALK* (lung) Unclear	FFPE DNA Fluorescence in situ	Nonsmall cell lung cancer Abbot Labs Chromosome rearrangements 136	Vysis LSI 3′-*ALK* SO: 100% 95% CI, (98.5 to 100.0) Vysis LSI 5′-*ALK* SGn: 100% 95% CI, (98.5 to 100.0)	Vysis LSI 3′-*ALK* SO: 100% 95% CI, (97 to 100.0) Vysis LSI 5′-*ALK* SGn: 100% 95% CI, (97 to 100.0)	Yes Median Kappa score: 0.92 (range: 0.85 to 0.98)
Angulo, 2013[50] Test-retest *EGFR* (lung) Low	FFPE DNA PCR followed by *therascreen EGFR* Mutation Kit; Sanger sequencing	Nonsmall cell lung cancer Histology: Carcinomas NOS (23.5%) Squamous cell carcinomas (10.3%) Adenocarcinomas (64%) Large cell carcinomas (2.2%) Authors' lab(s) *EGFR* mutations at exons 19 to 21 136 samples	Exon 19 deletion: 100% Exon 21 L858R: 100% Exon 20 insertion: 67.75% All mutations :94.7%	Exon 19 deletion: 100% Exon 21 L858R: 100% Exon 20 insertion: 100% All mutations : 100%	No NA
Bando, 2010[34] Validation *KRAS* (colorectal) Medium	FFPE DNA Direct (Sanger) sequencing; *therascreen KRAS* Mutation Kit: Allele-specific PCR with Scorpion fluorescent probes (ARMS/S); *KRAS* Strip-Assay: Reverse hybridization (RH)	CRC Authors' lab(s) *KRAS* mutations at codons 12 and 13 100	RH: 51/74 (69%) ARMS/S: 56/74 (76%)	RH: 25/26 (96%) ARMS/S: 26/26 (100%)	No NA

Table 6. Results of included studies reporting on analytic validity, by test and cancer (continued)

Author, Year, Design, Test (Primary Site), Risk of Bias	Tissue Sample Requirements, Type of Analyte, Measure Technique	Neoplasms, Lab Reporting Results, Test Measure, Sample Size	Marker Sensitivity	Marker Specificity	Cross-Lab Validity Checked, Degree of Cross-Lab Variation
Beau-Faller, 2011[35] Validation *EGFR* (lung) Low	FFPE and frozen DNA Direct or nested Sanger sequencing; each center used its own standard procedure.	Nonsmall cell lung cancer NR *EGFR* mutations at exons 18 to 21 74	False positive results, median (range) Exon 19: 0% (0–27%) Exon 21: 17% (0–37%) False positive results, number of centers with false positive rate Exon 19: 0%–9/15 >0%–<10%: 1/15 ≥10%: 5/15 Exon 21: 0%: 7/15 >0–<10%: 0/15 ≥10%–8/15	False negative results, median (range) Exon 19: 2% (0–9%) Exon 21: 3% (0–6%) False negative results, number of centers with false positive rate Exon 19: 0%: 6/15 >0–<10%: 9/15 ≥10%: 0/15 Exon 21: 0%: 6/15 >0–<10%: 9/15 ≥10%: 0/15	Yes *EGFR* Exon 19: Median Kappa score: 0.52 (range: 0.23–0.73) *EGFR* Exon 21: Median Kappa score: 0.37 (range: 0.20–0.57)
Beau-Faller, 2009[36] Test-retest *KRAS* (lung) Low	Frozen DNA PNA-mediated PCR clamping Sanger sequencing	Nonsmall cell lung cancer Authors' lab(s) *KRAS* mutations at codons 12 and 13 114	NR	NR	No NA
Beau-Faller, 2011[35] Validation *KRAS* (lung) Low	FFPE and frozen DNA Direct or nested sequencing; each center used their own standard procedure.	Nonsmall cell lung cancer NR *KRAS* mutations at exon 2 74	False positive results, median (range) 8% (0–25%) False positive results, number of centers with false positive rate 0%–5/15 >0%–<10%: 4/15 ≥10%: 6/15	False negative results, median (range) 9% (2–17%) False negative results, number of centers with false positive rate 0%: 0/15 >0%–<10%: 8/15 ≥10%: 7/15	Yes Median Kappa score: 0.39 (range: 0.15–0.66)

Table 6. Results of included studies reporting on analytic validity, by test and cancer (continued)

Author, Year, Design, Test (Primary Site), Risk of Bias	Tissue Sample Requirements, Type of Analyte, Measure Technique	Neoplasms, Lab Reporting Results, Test Measure, Sample Size	Marker Sensitivity	Marker Specificity	Cross-Lab Validity Checked, Degree of Cross-Lab Variation
Clark-Langone, 2010[37] Test-retest Oncotype DX (colorectal) Medium	FFPE RNA RT-PCR of 12-gene Recurrence Score Assay	Stage II adenocarcinoma and mucinous carcinoma Authors' lab(s) Expression levels NR	NR	NR	No NA
Cronin, 2007[38] Test-retest Oncotype Dx (breast) Unclear	FFPE RNA RT-PCR of 21-gene Recurrence Score Assay	Node-negative, estrogen receptor–positive breast cancer Vendor's lab Expression levels NR	NR	NR	
Delahaye, 2013[39] Test-retest MammaPrint (breast) Medium	Fresh tissue RNA Microarray	Early-stage, invasive breast cancer Vendor's labs Expression levels N = 100 (cross-lab validation) N = 302 (PPV and NPV)	DMFS PPV (95% CI) (5 years): 0.22 (0.16 to 10.28) Overall survival PPV (95% CI) (10 years): 0.29 (0.22 to 20.35)	DMFS NPV (95% CI) (5 years): 0.95 (0.91 to 90.99) [see comment bubble] Overall survival NPV (95% CI) (10 years): 0.90 (0.85 to 80.96)	Yes 99%

Table 6. Results of included studies reporting on analytic validity, by test and cancer (continued)

Author, Year, Design, Test (Primary Site), Risk of Bias	Tissue Sample Requirements, Type of Analyte, Measure Technique	Neoplasms, Lab Reporting Results, Test Measure, Sample Size	Marker Sensitivity	Marker Specificity	Cross-Lab Validity Checked, Degree of Cross-Lab Variation
Feigelson, 2012[40] KRAS (colorectal) Low	FFPE DNA PCR amplification followed by Direct Sanger sequencing, PCR amplification followed by standard bidirectional sequencing, PCR amplification followed by sequencing, Single nucleotide primer extension with fragment analysis by capillary electrophoresis using a modified SNaPshot assay, or Qualitative real time PCR.	CRC (18 adenocarcinoma, 2 carcinoma) Genzyme, Clarient, Quest Diagnostics, Henry Ford Health System & Molecular and Medical Genetics-Oregon Health and Science University KRAS mutations at codons 12 and 13 20	False positive results, number of centers with false positive rate 0%: 3/5 5%: 2/5	False negative results, number of centers with false positive rate 0%: 4/5 5%: 1/5	Yes 90% were concordant across all five laboratories
Gao, 2010[41] Validation *KRAS* (colorectal) Unclear	FFPE DNA Dideoxy sequencing, *KRAS* StripAssay and pyrosequencing	CRC Authors' lab(s) *KRAS* mutation—exon 2 100	Pyrosequencing=5% *KRAS* strip assay=1% dideoxy=15%	NR	No NA

Table 6. Results of included studies reporting on analytic validity, by test and carcinoma (continued)

Author, Year, Design, Test (Primary Site), Risk of Bias	Tissue Sample Requirements, Type of Analyte, Measure Technique	Neoplasms, Lab Reporting Results, Test Measure, Sample Size	Marker Sensitivity	Marker Specificity	Cross-Lab Validity Checked, Degree of Cross-Lab Variation
Gonzalez de Castro, 2012[42] Test-retest *KRAS* (colorectal) Low	FFPE DNA Cobas *EGFR* Mutation Test (AS-PCR) *therascreen EGFR*29 Mutation Kit (ARMS); 2× bidirectional; Sanger sequencing	CRC 2 clinical site labs *KRAS* mutations at codons 12 and 13 115	Cobas *KRAS* and Sanger Sequencing (N=113): PPA=98.2%	Cobas *KRAS* and Sanger Sequencing (N=113): NPA=89.7%	Yes Cobas *KRAS* test reproducibility between the two sites:110/112 (98.2%) produced concordant results
Hancer, 2011[43] Cohort *KRAS* (colorectal) Unclear	FFPE DNA *therascreen KRAS* kit Entrogen *KRAS* mutation analysis kit Dideoxy sequencing,	Adenocarcinomas of the colon and the rectum Authors' lab(s) *KRAS* mutation—exon 2 64	NR	NR	No NA
Jancik, 2012[44] Test-retest *KRAS* (lung) High	Frozen DNA Direct sequencing, Pyrosequencing, and the *therascreen* DxS and KRAS StripAssay kits All of the above as well as high-resolution melting analysis (HRM)	Nonsmall cell lung cancer Authors' lab(s) *KRAS* mutations at codons 12 and 13 131	*therascreen* DxS kit: 95% KRAS StripAssay: 90% HRM: 70% Pyrosequencing: 48% Sequencing: 29%.	*therascreen* DxS kit, sequencing, and pyrosequencing: 100% HRM: 98% KRAS StripAssay: 95%	No NA

Table 6. Results of included studies reporting on analytic validity, by test and carcinoma (continued)

Author, Year, Design, Test (Primary Site), Risk of Bias	Tissue Sample Requirements, Type of Analyte, Measure Technique	Neoplasms, Lab Reporting Results, Test Measure, Sample Size	Marker Sensitivity	Marker Specificity	Cross-Lab Validity Checked, Degree of Cross-Lab Variation
Kobunai, 2010[45] Test-retest *KRAS* (colorectal) Low	Frozen DNA Peptide nucleic acid (PNA)-clamp real-time PCR Sanger sequencing	CRC Authors' lab(s) *KRAS* mutations at codons 12 and 13 224	NR	NR	No NA
Lopez-Rios, 2013[46] Test-retest *EGFR* (lung) Low	FFPE DNA Cobas *EGFR* Mutation Test (AS-PCR); *therascreen EGFR*29 Mutation Kit (ARMS); 2× bidirectional; Sanger sequencing	Nonsmall cell lung cancer 2 clinical site labs *EGFR* mutations at exons 18 to 21 124	AS-PCR test and Sanger: (N=113): PPA of 98.8%	AS-PCR test and Sanger: (N=113): NPA of 79.3%	Yes AS-PCR test reproducibility between the two sites: 122/123 (99.2%) produced concordant results
Mancini, 2010[47] Test-retest *BRAF* (colorectal) Medium	Frozen DNA PCR: Cold PCR—sensitivity then evaluated by HRM analysis and Sanger sequencing	Sporadic CRC Authors' lab(s) *BRAF* mutations at exon 15 117	NR	NR	No NA
Mancini, 2010[47] Test-retest *KRAS* (colorectal) Medium	Frozen DNA PCR: Cold PCR—sensitivity then evaluated by HRM analysis and sequencing	Sporadic CRC Authors' lab(s) *KRAS* mutations at codons 12 and 13 117	NR	NR	No NA

Table 6. Results of included studies reporting on analytic validity, by test and carcinoma (continued)

Author, Year, Design, Test (Primary Site), Risk of Bias	Tissue Sample Requirements, Type of Analyte, Measure Technique	Neoplasms, Lab Reporting Results, Test Measure, Sample Size	Marker Sensitivity	Marker Specificity	Cross-Lab Validity Checked, Degree of Cross-Lab Variation
Naoki, 2011[51] Test-retest EGRF (lung) Low	FFPE and frozen DNA PCR: PCR-invader method; Sanger sequencing	Nonsmall cell lung cancer BML *EGFR* mutations at exons 18 to 21 54	94.44% (derived from study)	79.17% (derived from study)	No NA
Pang, 2011[48] Validation *KRAS* (colorectal) High	FFPE DNA *KRAS* PCR	Stage IV colorectal adenocarcinoma Authors' lab(s) *KRAS* mutation—exons 2 and 3 11	NR	NR	No NA
Pang, 2011[48] Validation *BRAF* (colorectal) High	FFPE DNA *BRAF* PCR	Stage IV colorectal adenocarcinoma Authors' lab(s) *BRAF* mutation—exon 15 11	NR	NR	No NA
Poulet, 2012[52] Test-retest MammaPrint (breast) Unclear	Frozen DNA Microarray	ER+, HER2− early breast cancer Authors' lab(s) Cluster analysis 67	NR	NR	No NA

Table 6. Results of included studies reporting on analytic validity, by test and carcinoma (continued)

Author, Year, Design, Test (Primary Site), Risk of Bias	Tissue Sample Requirements, Type of Analyte, Measure Technique	Neoplasms, Lab Reporting Results, Test Measure, Sample Size	Marker Sensitivity	Marker Specificity	Cross-Lab Validity Checked, Degree of Cross-Lab Variation
Poulet, 2012[52] Test-retest Oncotype DX (breast) Unclear	Frozen RNA RT-PCR of 12-gene Recurrence Score Assay	ER+, HER2− early breast cancer Authors' lab(s) Expression levels 67	NR	NR	No NA
Sriram, 2011[53] Cohort *EGFR* (lung) Low	Frozen DNA ME-PCR; HRM Sanger sequencing	Nonsmall cell lung cancer NR *EGFR* mutations (exon 19 deletion and exon 21 L858R) 522 tumor tissue and 64 matched serum samples	ME-PCR:100% HRM: 100%	ME-PCR: 99% HRM: 100%	No NA
Van't Veer, 2002[49] Validation MammaPrint (breast) Medium	Frozen DNA Microarray	Breast cancer Authors' lab(s) Cluster analysis 78 in development set, 19 in validation set	NR	NR	No NA

Abbreviations: ARMS = Amplification Refractory Mutation System; AS = Allele-Specific; BML = Bio Medical Laboratories (Tokyo, Japan); *BRAF* = gene name; DNA = deoxyribonucleic acid; *EGFR* = gene name; ER = estrogen receptor; FFPE = formalin-fixed, paraffin-embedded; HER2 = Human Epidermal Growth Factor Receptor 2, also known as (Neu); HRM=high-resolution melting; *KRAS* = gene name; ME = mutant enriched; N = number of samples; NA = not applicable; NOS = not otherwise specified; NPA = negative percent agreement; NR = not reported; PCR = polymerase chain reaction; PNA= peptide nucleic acid; PPA = positive percent agreement; RH = reverse hybridization; SGn = SpectrumGreen; SO = SpectrumOrange.

Data from the College of American Pathologists' for *EGFR* mutations, *KRAS* mutations, *BRAF* mutations, microsatellite instability for colorectal cancer, and UroVysion cytogenetics for urinary bladder cancer support the analytic validity of these tests (see data in relevant sections below).

Breast Cancer: MammaPrint

Characteristics of Included Studies Assessing Analytic Validity of MammaPrint

MammaPrint uses a 70-gene signature to classify breast carcinoma patients into those with a good or poor prognosis, based on risk of distant metastasis.

One study by Poulet[52] was rated unclear in terms of RoB and is excluded from the description of results below.

Two MammaPrint studies were rated as low or medium RoB (Table 5).[39,49] van't Veer[49] developed the 70-gene signature prognostic assay (now known as MammaPrint) for risk of recurrence in early-stage breast cancer, and tested prediction to metastases in 97 patients. Delahaye,[39] affiliated with Agendia NV, studied the analytical performance of MammaPrint, including reproducibility, precision, repeatability, tumor heterogeneity, and inter-lab reproducibility.

MammaPrint: Analytic Validity

Both MammaPrint studies indicated that the MammaPrint test is precise, repeatable (98.5 to 99 percent), and reproducible for prediction of metastasis in breast cancer (Table 6). The largest contributor to assay variation was intratumor heterogeneity, which is significantly greater than the technical variation in the MammaPrint test.

Nonsmall Cell Lung Carcinoma: *EGFR* and *KRAS* Mutations

Characteristics of Included Studies Assessing Analytic Validity of *EGFR* Mutation

We reviewed the analytic validity of tests that detected mutations in the *EGFR* gene. All studies looked at mutations in the gene within exons 18, 19, and/or 21.

We rated 5 studies reporting analytic validity of *EGFR* testing for lung cancer as having low RoB (Table 5). Angulo[50] compared *therascreen EGFR* mutation screening to direct sequencing of *EGFR* in FFPE lung tumor tissue. Lopez-Rios[46] compared the Cobas *EGFR* Mutation Test and *therascreen EGFR* Mutation Test with direct sequencing of *EGFR* in FFPE lung carcinoma tissue. Sriram[53] compared mutant-enriched-PCR and high-resolution melting methods in frozen lung tissue, a subset (97 of 522 samples) of which were previously DNA sequenced in the *EGFR* gene. Naoki[51] compared the PCR-invader method with direct DNA sequencing in FFPE lung tissue and pleural and pericardial effusions. Beau-Faller[35] compared several PCR-based methods to direct DNA sequencing of *EGFR* in FFPE lung tissue across 15 centers.

Also, we received results of proficiency testing from The College of American Pathologists (CAP) to address intralab reproducibility of *EGFR* mutation testing.

EGFR Mutation: Analytic Validity

In general, all five *EGFR* testing studies for lung cancer compared various PCR-based methods against one another or against DNA sequencing in FFPE tissue (Table 6). All of these studies found that, compared with DNA sequencing, PCR-based methods of screening for *EGFR* mutations had a lower limit of detection and thus were more sensitive in samples with <20% carcinoma. However, because PCR-based methods are based on known mutations found between exons 18 and 21 of the *EGFR* gene, DNA sequencing is a better method for identifying novel mutations and mutations elsewhere in the gene.

The CAP sends proficiency test *EGFR* unknowns to CLIA-approved US clinical laboratories or International clinical laboratories for assessing nationwide interlab reproducibility. The three most recent surveys[54] found accuracy rates of 93 percent (122/131; EGFR-B, 2012), 96 percent (157/164; EGFR-A, 2013), and 96 percent (195/204; EGFR-B, 2013), for an average diagnostic accuracy of 94 percent (474/499).

Characteristics of Included Studies Assessing Analytic Validity of *KRAS* Mutation in Nonsmall Cell Lung Carcinoma

We reviewed the analytic value of tests that detected mutations in the *KRAS* gene. The studies looked at mutations at codons 12 and 13 or on exon 2 in the *KRAS* gene but not at codon 61.

One study by Jancik[44] was rated as having a high RoB and is excluded from the description of results below.

We rated two *KRAS* mutant lung cancer studies as having low RoB (Table 5). Beau-Faller (2009)[36] compared peptide-nucleic-acid-mediated PCR clamping to direct DNA sequencing in frozen lung tissue. Beau-Faller (2011)[35] compared several PCR-based methods to direct DNA sequencing of *KRAS* in FFPE lung tissue across 15 centers.

Also, we received results of proficiency testing from CAP to address intralab reproducibility of *KRAS* mutation testing.

KRAS Mutation for Lung Cancer: Analytic Validity

Both of the *KRAS* mutant lung cancer studies (Table 6) found that, compared with DNA sequencing, PCR-based methods of screening for *KRAS* mutations had a lower limit of detection, and thus were more sensitive when the samples contained <20% carcinoma.

CAP sends proficiency test *KRAS* unknowns to CLIA-approved US clinical laboratories or International clinical laboratories for assessing nationwide interlab reproducibility. The three most recent surveys[55] found accuracy rates of 98 percent (194/197; KRAS-B, 2012), 98 percent (206/209; KRAS-A, 2013), and 98 percent (211/215; KRAS-B, 2013), for an average diagnostic accuracy of 98 percent (611/621).

Characteristics of Included Studies Assessing Analytic Validity of *ALK* Translocation

There were no published studies that provided any information about the analytic validity of the ALK Translocation test. Abbot Labs, 2011[32] has information provided with their Vysis ALK Break Apart FISH Probe Kit literature on specific performance characteristics, including analytical sensitivity and specificity, tissue reproducibility, and external reproducibility (Tables 5 and 6). This work was rated unclear in terms of RoB and is excluded from the description of results.

Colorectal Carcinoma:

Characteristics of Included Studies Assessing Analytic Validity of *BRAF* Mutation

The *BRAF* mutation tests being examined in this report screen for the V600E mutation in the *BRAF* gene.

One study by Pang (2011)[48] was rated as having a high RoB and is excluded from the description of results below.

A single *BRAF* CRC study had a rating of medium RoB (Table 5). Mancini[47] compared a novel lower denaturation temperature PCR (COLD-PCR) with the more traditional high-resolution melting (HRM) PCR method in screening for *BRAF* c.1799 T>A (p.V600E) mutation.

Also, we received results of proficiency testing from CAP to address intralab reproducibility of *BRAF* mutation testing.

BRAF Mutation: Analytic Validity

Mancini[47] found that COLD-PCR was more sensitive than HRM-PCR for detecting the *BRAF* mutation (Table 6).

The College of American Pathologists sends proficiency test *BRAF* unknowns to CLIA-approved U.S. clinical laboratories or International clinical laboratories, an excellent mechanism for assessing inter-lab reproducibility. The three most recent surveys[56] found accuracy rates of 100% (140/140; BRAF-B, 2012), 98% (192/195; BRAF-A, 2013), and 98% (196/200; BRAF-B, 2013), for an average diagnostic accuracy of 99% (528/535).

Characteristics of Included Studies Assessing Analytic Validity of *KRAS* Mutation in Colorectal Carcinoma

The genetic test for *KRAS* mutations described here checks for mutations in codons 12 and 13 in the *KRAS* gene but not in codon 61.

One study by Pang[48] was rated as having a high RoB, and two studies—Gao[41] and Hancer[43]—were rated as having unclear RoB and are excluded from the description below.

We rated five *KRAS* mutant CRC studies as having low to medium RoB (Table 5). Mancini[47] compared COLD-PCR with the HRM PCR method in screening for *KRAS* mutations in frozen colorectal tissue. Kobunai[45] compared peptide nucleic acid-clamp PCR with direct sequencing in frozen colorectal tissue. Gonzalez de Castro[42] compared the cobas *KRAS* Mutation Test and the Qiagen *therascreen KRAS* Kit methods to direct *KRAS* sequencing in FFPE colorectal tissue. Bando[34] compared the *KRAS* StripAssay and *therascreen KRAS* Mutation kit with direct *KRAS* sequencing. Feigelson[40] compared five different *KRAS* mutation testing regimens for comparability and consistency across five laboratories.

Also, we received results of proficiency testing from CAP to address intralab reproducibility of *KRAS* mutation testing.

KRAS Mutation for Colorectal Carcinoma: Analytic Validity

All of these studies found that, compared with DNA sequencing, PCR-based methods of screening for *KRAS* mutations had a lower limit of detection, and thus were more sensitive in samples with <20% carcinoma (Table 6).

CAP sends proficiency test *KRAS* unknowns to CLIA-approved US clinical laboratories or International clinical laboratories for assessing nationwide interlab reproducibility. The three

most recent surveys[55] found accuracy rates of 98 percent (194/197; KRAS-B, 2012), 98 percent (206/209; KRAS-A, 2013), and 98 percent (211/215; KRAS-B, 2013), for an average diagnostic accuracy of 98 percent (611/621).

Characteristics of Included Studies Assessing Analytic Validity of MSI

We found no individual published studies meeting our inclusion criteria that reported eligible information on analytic validity of the microsatellite instability (MSI) test for CRC.

We received results of proficiency testing from CAP to address intralab reproducibility of MSI testing.

MSI for Colorectal Carcinoma: Analytic Validity

CAP sends proficiency test MSI unknowns to CLIA-approved US clinical laboratories or International clinical laboratories for assessing nationwide interlab reproducibility. The three most recent surveys[57] found accuracy rates of 100 percent (89/89; MSI-B, 2012), 99 percent (96/97; MSI-A, 2013), and 98 percent (103/105; MSI-B, 2013), for an average diagnostic accuracy of 99 percent (288/291).

Characteristics of Included Studies Assessing Analytic Validity of Oncotype DX (for Breast and Colon)

Oncotype DX Breast and Oncotype DX Colon are mRNA abundance assays performed on formalin-fixed paraffin-embedded tissue. They are not intended to act as surrogate tests for identifying underlying gene mutations. Selected mRNA abundance differences have been correlated with known clinical outcomes and are now used to predict risk of recurrence and to guide adjuvant therapy use in new patients who have undergone resection of their primary carcinomas for cure. Oncotype DX Breast uses a 21-gene mRNA expression signature and assigns a recurrence risk score (RS) ranging from 0 to 100 for each patient. Oncotype DX Colon uses a 12-gene mRNA expression signature and assigns an RS ranging from 0 to 100 for each patient.

The Cronin lab at Genomic Health measured intralaboratory detectability, dynamic range, and reproducibility for assays on this set of 21 mRNAs for Oncotype DX Breast.[38] This study was rated as having unclear RoB (Table 5). Published data on Oncotype DX Colon by Clark-Langone,[37] affiliated with the Cronin lab and referencing the above paper, provided similar analytical validity data for the 12-gene Oncotype DX Colon assay.

Oncotype DX: Analytic Validity

The data from Cronin's group at Genomic Health[38] found high intralab reproducibility for Oncotype quantitative RT-PCR mRNA abundance measurements relevant to the Oncotype DX tests for breast and colon carcinoma. Clark-Langone[37] reported high analytic validity and precision for the Oncotype DX Colon assay (Table 6). No references were found to estimate interlaboratory reproducibility, because this assay is not performed outside of Genomic Health.

Bladder Cancer: UroVysion

Characteristics of Included Studies Assessing UroVysion

UroVysion is a fluorescence in situ hybridization (FISH) test of exfoliated urothelial cells that has been shown to be sensitive in terms of diagnosing urothelial cancer.

We found no individual published studies meeting our inclusion criteria that reported eligible information on analytic validity of the UroVysion test for bladder cancer.

We received results of proficiency testing from CAP to address intralab reproducibility of UroVysion testing.

UroVysion: Analytic Validity

CAP sends proficiency test UroVysion unknowns to CLIA-approved US clinical laboratories or International clinical laboratories for assessing nationwide interlab reproducibility. The four most recent surveys[58] found accuracy rates of 99 percent (168/170; UroVysion-A, 2013), 99 percent (168/170; UroVysion-B, 2013), 99 percent (191/192; UroVysion-C, 2013), and 100 percent (193/193; UroVysion-D, 2013), for an average diagnostic accuracy of 100 percent (552/555).

Clinical Validity: Breast Cancer: MammaPrint and Oncotype DX

Characteristics of Included Studies Assessing Clinical Validity of MammaPrint

We found 11 studies[49,59-68] that reported on the prognostic value of the RS from MammaPrint for RR, CSS, or OS in patients with breast cancer (Table 7). All were cohort studies. Sample sizes ranged from 89 to 964. Median followup was 3 to 10 years. Eight out of 10 studies were conducted in the Netherlands either exclusively by the group that developed the signature or in collaboration with other European countries. One study was conducted in the United States,[61] and one was conducted in France, Sweden, and the United Kingdom.[60]

All studies compared outcomes of patients who had a good prognosis signature with those who had a poor prognosis signature. Age of the women in the studies for which age is reported was approximately 50 years, although a couple of studies included women who were in their twenties. Race or ethnicity was not reported in any of the studies.

There were some differences in the populations enrolled in the included studies. Differences were in stage and ER, node positivity, and age. Three studies restricted the sample to node-negative cancers,[59,60,65] a couple included cases with one to three positive nodes,[63,67] one looked at patients with four to nine positive nodes[68]and two included stages I through III,[62,63] whereas the others restricted the study to stage I or II.

Table 7. Characteristics of included studies: MammaPrint for breast cancer

Author, Year Study Type Risk of Bias	N Length of Followup	Country(ies)	Disease Stage(s) Other Tumor/ Disease Characteristics	Study Groups	Race Ethnicity	Overall Age (years) % Female
Bueno-de-Mesquita 2009[59] Cohort Low	151 Median 10.2 years (0.7–21.3)	The Netherlands	Early stage Node-negative breast cancer, tumor diameter pT1–2.	Good prognosis signature Poor prognosis signature	NR NR	Mean (range): 47 (27–55)
Buyse, 2007[60] Cohort Unclear	307 Median: 13.6 years	France, Sweden, and United Kingdom	I–II Node negative	Good prognosis Poor prognosis	NR NR	Median: 58 100%
Iwamoto, 2011[61] Cohort Unclear	228 Median 56.4 (5.9 to 60) months	United States	I–III ER-positive and -negative cancers as well as low and high histologic grade tumors	Good prognosis Poor prognosis	NR NR	51.9 (26–79) NR
Knauer, 2010[62] Cohort Low	89	The Netherlands, Austria, and Belgium	I–III Unilateral HER2 positive invasive breast carcinoma, no chemotherapy, no trastuzumab	Good prognosis Poor prognosis	NR NR	Median (range): 50 (28–79) 100%
Mook, 2009[63] Cohort Low	241	The Netherlands, Italy	II–III (T stage 1–3 with 1–3 positive lymph nodes)	Good prognosis Poor prognosis	NR NR	NR NR
Mook, 2010[64] Pooled analysis of multiple cohorts Low	964 Median (range): 7.1 (0.2–25.2) years	The Netherlands	pT1 including 1a, 1b, and 1c tumors	Good prognosis Poor prognosis	NR NR	NR NR
Mook, 2010[65] Cohort Medium	148 Median (range): 375.1 (41.7 to 922.2) weeks	The Netherlands	I–II Node negative	Good prognosis Poor prognosis	NR NR	Range 55–70 100%
Nuyten, 2008[66] Cohort Medium	144 Median (range): 10.2 (0.05 to 21.7) years	The Netherlands	II Node positive	Good prognosis Poor prognosis	NR NR	NR NR

Table 7. Characteristics of included studies: MammaPrint for breast cancer (continued)

Author, Year Study Type Risk of Bias	N Length of Followup	Country(ies)	Disease Stage(s) Other Tumor/ Disease Characteristics	Study Groups	Race Ethnicity	Overall Age (years) % Female
Saghatchian, in press[68] Cohort Medium	173 Median, 7.9 years	The Netherlands, Italy	Primary invasive breast cancer with 4 – 9 positive nodes, T1-3, estrogen receptor +/-, progesterone receptor +/-, HER2 +/-	Genomic high risk Genomic low risk		Age for each group, mean (SD): GHR = 49.1 (9.7); GLR = 51.4 (9.5 100%
Van't Veer, 2002[49] Cohort Medium	98	The Netherlands	Sporadic breast cancer 55 years or younger, 18 cases of BRCA1 and 2 BRCA2	Good prognosis Poor prognosis	NR NR	All patients were younger than 55 years at diagnosis 100%
Van de Vijver, 2002[67] Cohort Low	295 Median (range): 7.8 years (0.05 to 18.3) years (207 patients without metastasis as the first event) Median (range): 2.7 (0.3 to 14.0) years (88 patients with metastasis as the first event). Median (range): 6.7 (0.05 to 18.3) years (all 295 patients)	The Netherlands	I-II	Good prognosis Poor prognosis	NR NR	All patients were younger than 53 years 100%

Abbreviations: HER2 = Human Epidermal Growth Factor Receptor 2, also known as Neu; MUT = mutation; N = number; NR = not reported; SD = standard deviation.

MammaPrint: Risk of Recurrence

Six cohort studies rated as low or medium RoB reported RR (total N=1,913).[59,62-64,67,68] All studies used distant metastasis-free survival (DMFS) instead of recurrence-free survival (local and distant recurrence) as their outcome. All six reported on the prognostic value of MammaPrint after controlling for traditional prognostic factors such as stage, size, and differentiation, for example. One study used the composite score from Adjuvant! Online—an online program that combines traditional prognostic factors to calculate an RS.[69] All studies concluded that patients with a poor prognosis signature had a higher risk of distant metastasis compared with patients with a good prognosis signature. The hazard ratios (HRs) in these studies ranged from 2.43 to 5.8, and all the studies had overlapping 95% confidence intervals (Table 8).

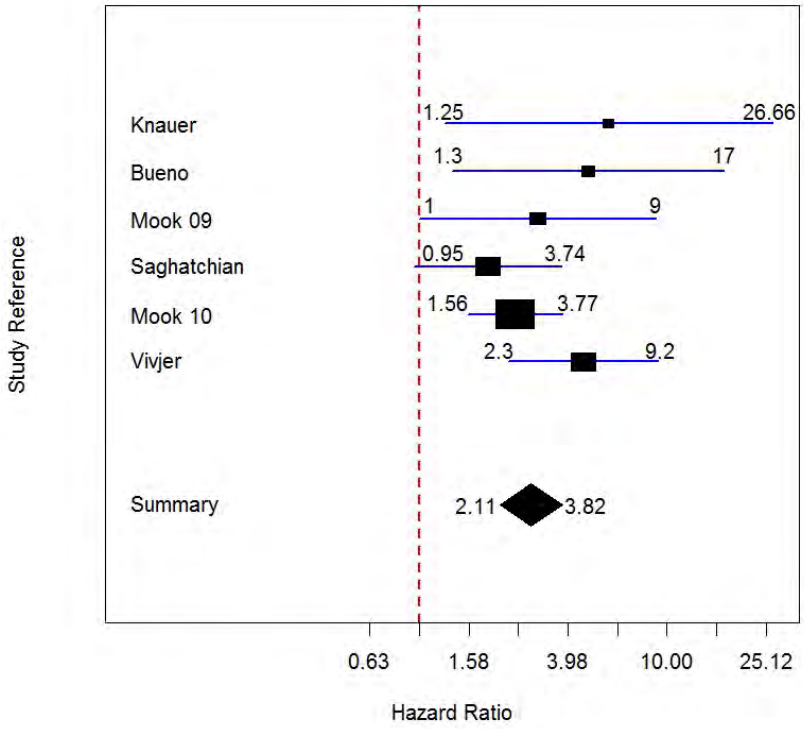
Table 8. Breast Cancer: MammaPrint risk of distant metastasis-free survival

Author, Year, Design, N, Risk of Bias	Adjusted HR (95% CI), p-value	Variables Used in Multivariate Model
Knauer, 2010[62] Cohort 89 Low	DMFS HR: 5.8 (1.25 to 26.66) p=0.025	Age at diagnosis, tumor size, number of positive lymph nodes, histological grade (1/2 vs. 3), ER status, progesterone receptor (PR) status, adjuvant hormonal therapy
Bueno-de-Mesquita 2009[59] Cohort 151 Low	DMFS RS in NKI-RdGG series HR: 4.8 (1.3 to 17) RS in updated validation series HR: 5.3 (95% CI: 2.4 to 12)	Performance of 70-gene prognosis signature vs. performance of predictor with results for 4 different models; results from Adjuvant! Online
Mook, 2009[63] Cohort 241 Low	DMFS HR: 3.0 (1.0 to 9.0) p=0.05	Age (years); number of positive nodes: 2 vs. 1 and 3 vs. 1; tumor size (20 mm vs. ≤20 mm); histological grade: moderate vs. good, poor vs. good; ER status; HER2 receptor status; surgery (mastectomy vs. breast conservation therapy [BCT]) chemotherapy; endocrine therapy; prognosis signature (poor vs. good signature)
Mook, 2010[64] Pooled analysis of several cohorts 964 Medium	DMFS HR: 2.43 (1.56 to 3.77) p<0.001	Age, histology, tumor size, nodal status, grade, ER status, HER2 status, type of surgery, hormonal therapy (yes/no), chemotherapy (yes/no), 70-gene signature
Saghatchian, in press[68] Cohort 173 Medium	DMFS MammaPrint, low risk vs. high risk, main analysis HR: 1.888 (0.953 to 3.739) p=0.068 DMFS MammaPrint, low risk vs. high risk, subgroup analysis (N=129 women with 4 to 9 positive nodes) 2.698 (1.267 to 5.748) p=0.010	Main analysis: Age, invasive ductal carcinoma, number of positive nodes, grade, ER status, PR status, and HER2 status Subgroup analysis: Age, invasive ductal carcinoma, number of positive nodes, grade
Van de Vijver, 2002[67] Cohort 295 Low	DMFS HR: 4.6 (2.3 to 9.2) p<0.001	Age, lymph node status, diameter of tumor, tumor grade, vascular invasion, estrogen receptor status, mastectomy, chemotherapy, hormonal treatment

Abbreviations: BCT = breast conservation therapy; CI = confidence interval; ER =estrogen receptor; HER2 = Human Epidermal Growth Factor Receptor 2, also known as Neu; HR = hazard ratio; mm = millimeter; N = number; N+ = number positive; NKI-RdGG = the name of a clinical trial; p = probability; PR = progesterone receptor; RS = risk score.

Using a fixed effects model, our meta-analysis found a greater risk of recurrence for the poor prognosis group than for the good prognosis group (HR, 2.84; 95% CI, 2.11 to 3.82; Figure 4).

Figure 4. Prognostic value of MammaPrint for risk of recurrence, meta-analysis of adjusted hazard ratios



MammaPrint: Cancer-Specific Mortality

Five studies (N=1,615) rated as medium RoB reported on CSS for MammaPrint.[62-65,68]

The reported HRs are from models that controlled for traditional prognostic factors such as histology, size, and nodal status. Mook (2010)[65] used Adjuvant! Online that combines various clinic pathological factors to create an RS; the remaining studies included the clinic pathological factors in the model. All studies reported that patients with a poor prognosis signature had a higher cancer-specific mortality rate than those with a good prognosis signature (Table 9).

Table 9. Breast cancer: MammaPrint cancer-specific survival

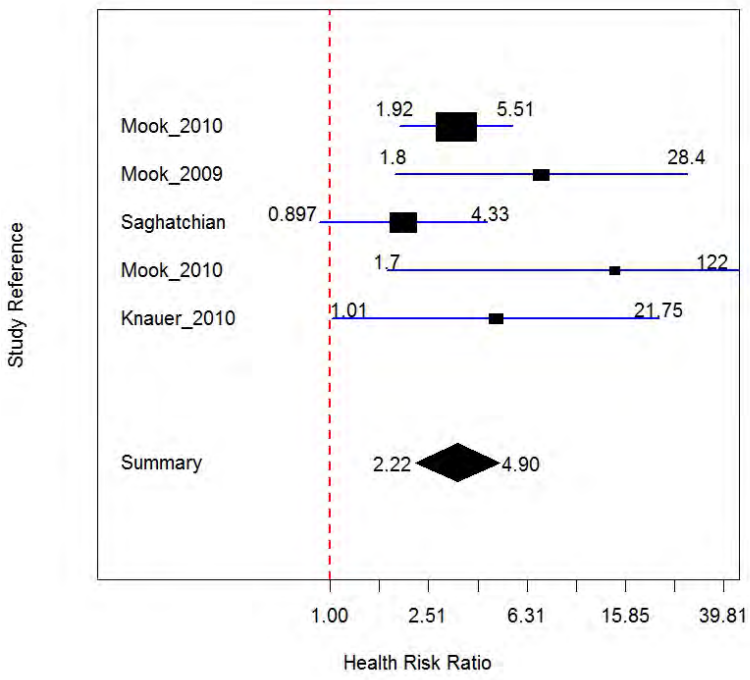
Author, Year, Design, Number of Patients, Risk of Bias	HR (95% CI),	p-value	Variables Used in the Multivariate Model
Knauer, 2010[62] Cohort 89 Medium	4.7 (1.01 to 21.75)	p=0.048	Age at diagnosis, tumor size, number of positive lymph nodes, histological grade (1/2 vs. 3), ER status, PR status, adjuvant hormonal therapy
Mook, 2010[65] Cohort 148 Moderate	14.4 (1.7 to 122) at 5 years	p=0.01	Adjuvant! Online score, which incorporates age, tumor size and grade, lymph node status, health status, hormone receptors
Mook, 2010[64] Pooled analysis of several cohorts 964 Moderate	3.25 (1.92 to 5.51)	p<0.001	Age, histology, tumor size, nodal status, grade, ER status, HER2 status, type of surgery, hormonal therapy (yes/no), chemotherapy (yes/no), 70-gene signature
Mook, 2009[63] Cohort 241 Low	7.2 (1.8 to 28.4)	p=0.005	Age (years), number of positive nodes: 2 vs. 1 and 3 vs. 1, tumor size (20 mm vs. ≤20 mm) Histological grade: moderate vs. good, poor vs. good, ER status, HER2 receptor status, surgery (mastectomy vs. BCT) chemotherapy, endocrine therapy, prognosis signature (poor vs. good signature)
Saghatchian, in press[68] Cohort 173 Medium	MammaPrint, low risk vs. high risk, main analysis 1.971 (0.897 to 4.330)	p=0.091	Main analysis: Age, invasive ductal carcinoma, number of positive nodes, grade, ER status, PR status, and HER2 status
	MammaPrint, low risk vs. high risk, subgroup analysis (N = 129 women with 4 to 9 positive nodes 2.674 (1.069 to 6.685)	p=0.035	Subgroup analysis: Age, invasive ductal carcinoma, number of positive nodes, grade

[a] calculated from years by abstractor

Abbreviations: BCT = breast conservation therapy; CI = confidence interval; ER = estrogen receptor; HER2 = Human Epidermal Growth Factor Receptor 2, also known as Neu; HR = hazard ratio; p = probability; PR = progesterone receptor.

Using a fixed effects model, our meta-analysis found a greater RR for the poor prognosis group than for the good prognosis group (HR, 3.3; 95% CI, 2.22 to 4.9) (Figure 5).

Figure 5. Prognostic value of MammaPrint for cancer-specific survival, meta-analysis of adjusted hazard ratios



MammaPrint: Overall Survival

Only one study[66]with a moderate RoB rating was available to assess the prognostic value of MammaPrint for overall survival (Table 10). The study included 144 patients and did not find a statistically significant association between test result and survival.

Table 10. Breast cancer: MammaPrint overall survival

Author, Year, Design, N, Risk of Bias	Adjusted Ratios (95% CI), p-value	Variables Used in Multivariate Model
Nuyten, 2008[66] Cohort N=144 Moderate	Death: HR:1.67 (0.73 to 3.82) p=0.23	Diameter, grade age; ER status; angio invasion; chemotherapy; hormonal therapy hypoxia-wound signature combination

Abbreviations: CI = confidence interval; ER = estrogen receptor; HR = hazard ratio; p = probability; N = number.

Characteristics of Included Studies Assessing the Clinical Validity of Oncotype DX

We included eight studies[70-77] that reported on the prognostic value of Oncotype DX Breast for RR, CSS, and OS in patients with breast cancer. Six were cohort studies with sample sizes that ranged from 338 to 1,231. Median followup was between 8 and 10 years. Two studies were case-control studies. Five studies were conducted in the United States, one in Japan, and one in

the United Kingdom. Race and ethnicity were not reported for most studies; one study reported enrolling 80 percent non-Hispanic White subjects,[71,72] and one reported enrolling 92 percent White subjects.[76]

All of the cohort studies used tissue collected during large randomized clinical trials. Dowsett[70] used tissue from the ATAC trial; Habel sampled cases and controls from the Kaiser Permanente Tumor registry. Paik (2004)[74] and Tang[76] report on the same 668 patients from the NSABP-14 trial. Mamounas[72] includes the 668 patients used in Paik (2004)[74] and Tang[76] in the 895 patients they report on in their paper. Solin[75] used tissue from the E2197 trial. One of the case-control studies identified 165 cases as those who died from breast cancer, and 401 controls matched by age, race, and calendar year[71]; the other case-control study used 10 cases who had distant metastases and age-matched controls who did not have metastases during the observation period.

Most of the studies included only ER+ patients.[72-74,77] Half of the included studies also restricted enrollment to node-negative subjects[72-74,76] (Table 11).

Table 11. Characteristics of included studies: Oncotype DX for breast cancer

Author, Year Study Type Risk of Bias	N Length of Followup	Country(ies)	Disease Stage(s) Other Tumor/ Disease Characteristics	Study Groups	Race Ethnicity	Overall Age (years) % Female
Dowsett, 2010[70] Cohort Medium	1,231 Median 8.5 years	United Kingdom	Stage NR ER+ breast cancer	RS was a continuous var[a]	NR NR	Mean 64.1 100%
Habel, 2006[71] Case-control Low	566 NR	United States	Stage NR Invasive breast cancer	Low (RS<18) Intermediate (RS 18–30) High (RS>31)	80% non-Hispanic White	NR 100%
Mamounas, 2010[72] Cohort Moderate	895 Median: 12.5 years	United States	Stage NR Node negative, ER+ breast cancer	Low (RS<18) Intermediate (RS 18–30) High (RS≥31)	NR NR	NR NR
Mamounas, 2012[73] Cohort Unclear	1,065 Median 11.2 years	NR	Stage NR Node positive, ER+ breast cancer	Low (RS<18) Intermediate (RS 18–30) High (RS≥31)	NR NR	NR NR
Paik 2004[74] Cohort Medium	668 NR	United States	Stage NR Node negative, ER+ breast cancer	Low (RS<18) Intermediate (RS 18–30) High (RS≥31)	NR NR	NR NR
Solin 2012[75] Cohort Medium	388 Median (range): 9.7 (3.7 to 11.6) years	United States	Stage NR 1–3 positive lymph nodes or negative lymph nodes with tumor size >1.0 cm	Local recurrence Local-regional recurrence	NR NR	NR 100%
Tang, 2011[76] Cohort Low	668 Median 14.3 years	United States	NR Node negative, ER+ breast cancer, tamoxifen treated	RS percentile[b]	White: 615 (92%) Black: 31 (5%) Others: 22 (3%) NR	NR 100%

Table 11. Characteristics of included studies: Oncotype DX for breast cancer (continued)

Author, Year Study Type Risk of Bias	N Length of Followup	Country(ies)	Disease Stage(s) Other Tumor/ Disease Characteristics	Study Groups	Race Ethnicity	Overall Age (years) % Female
Yorozuya, 2010[77] Case-control Medium	40 (10 cases), 30 controls Median: 232.3 weeks (cases)	Japan	Stage I or Iia, ER+ primary breast cancer	Low (RS<18) Intermediate (RS 18–30) High (RS≥31) (within 2 years)	NR NR	Cases mean (range): 49.1 (37 to 76) Controls mean (range): 50.9 (37 to 78) 100%

[a] Risk score was a continuous variable, with the HR for distant recurrence calculated relative to an increment of 50 units (e.g., the HR for Risk Score=55 vs. Risk Score=5), chosen to be consistent with prior clinical validation studies.

[b] RI-PCT had a range from 0 to 100; it was by 50 and rescaled to a range from 0 to 2 in regression analyses so that the associated HRs were comparable to those HRs associated with clinicopathologic factors.

Abbreviations: cm = centimeter; ER = estrogen receptor; MUT = mutation; N = number; NR = not reported; RS = risk score.

Oncotype DX: Risk of Recurrence

Six cohort studies[70,72,74-77] with low or medium RoB rating (total N=3,222 patients) and a case-control study with 40 patients (10 cases with recurrence and 30 controls) reported on the prognostic value of Oncotype for RR in breast cancer.

Dowsett,[70] Paik (2004),[74] Tang,[76] and Yorozuya[77] all used distant recurrence as the primary endpoint. Solin[75] and Mamounas[72] used loco or loco-regional recurrence (LRR) as the primary end point. All of the included studies reported on the prognostic value of Oncotype DX after controlling for traditional prognostic factors such as stage, size, and differentiation, for example. The number of variables in the models varied across the studies, and a couple looked at the effect of controlling for several combinations of prognostic factors (Table 12). A high RS was consistently shown to be a predictor of distant recurrence but not for LRR.

Table 12. Breast cancer: Oncotype DX risk of cancer recurrence (disease-free survival, recurrence-free survival, distant metastasis-free survival)

Author, Year, Design, Number of Patients, Risk of Bias	Adjusted Ratios(95% CI), p-values	Variables Used in Multivariate Model
Dowsett, 2010[70] Cohort 1,231 Moderate	Distant recurrence N0 patients: HR: 5.25 (2.84 to 9.73) p<0.001 N+ patients: HR: 3.47 (1.64 to 7.38) p=0.002	Tumor size (>2 vs. ≤2 cm); central grade (moderate vs. well, and poor vs. well); age (<65 vs. ≥65); positive nodes (≥4 vs. 1–3 nodes); positive nodes variable only included in analyses for N+ patients
Mamounas, 2010[72] Cohort 895 qwModerate	RS as a continuous variable calculated relative to an increment of 50 units: LRR HR: 2.16 (1.26 to 3.68**)** p=0.005 Intermediate vs. low risk: HR: 2.16 (0.98 to 4.75) p=0.143 High vs. low risk: HR: 1.67 (0.78 to 3.58) p=NR	Age (≥50 vs. <50); mastectomy vs. lumpectomy and radiation therapy; clinical tumor size (>2 vs. ≤2 cm); tumor grade (moderate vs. well); tumor grade (poor vs. well)

Table 12. Breast cancer: Oncotype DX risk of cancer recurrence (disease-free survival, recurrence-free survival, distant metastasis-free survival) (continued)

Author, Year, Design, Number of Patients, Risk of Bias	Adjusted Ratios(95% CI), p-values	Variables Used in Multivariate Model
Paik 2004[74] Cohort 668 Medium	RS Distant recurrence HR:3.21 (2.23 to 4.61) p<0.001	Age, tumor size, RS
Solin 2012[75] Cohort 388 Medium	NR NS for local or LRR	Chemotherapy arm, patient age, HR status, pathologic axillary lymph node status, histologic grade, pathologic T stage, biologic subtype, and 21-gene RS
Tang, 2011[76] Cohort 668 Low	Distant recurrence RS-PCT/50 Model 4: HR: 2.83 (95% CI: 1.91 to 4.18) p<0.001 Model 5: HR: 2.37 (95% CI, 1.58 to 3.55) p<0.001 Model 6: HR: 2.34 (95% CI, 1.56 to 3.5) p<0.001	Model 4: Adjuvant! Online score (RI) as a composite covariate representing common prognostic factors Model 5: included Adjuvant! Online score (RI); also included common prognostic factors as individual covariates including: age (>50 vs. ≤50); tumor size (cm); grade (moderate vs. well); grade (poor vs. well); RI-PCT/50 Model 6: included only individual prognostic factors as covariates including age (>50 vs. ≤50); tumor size (cm); grade (moderate vs. well); grade (poor vs. well); RI-PCT/50
Yorozuya, 2010[77] Case-control 40 (10 cases), 30 controls) Moderate	OR: 2.85 (95% CI: 0.07 to 115.5) p=0.579	Age at diagnosis; ER score; PgR score; RS 50 or more vs. RS<50; histological grade lymphatic invasion

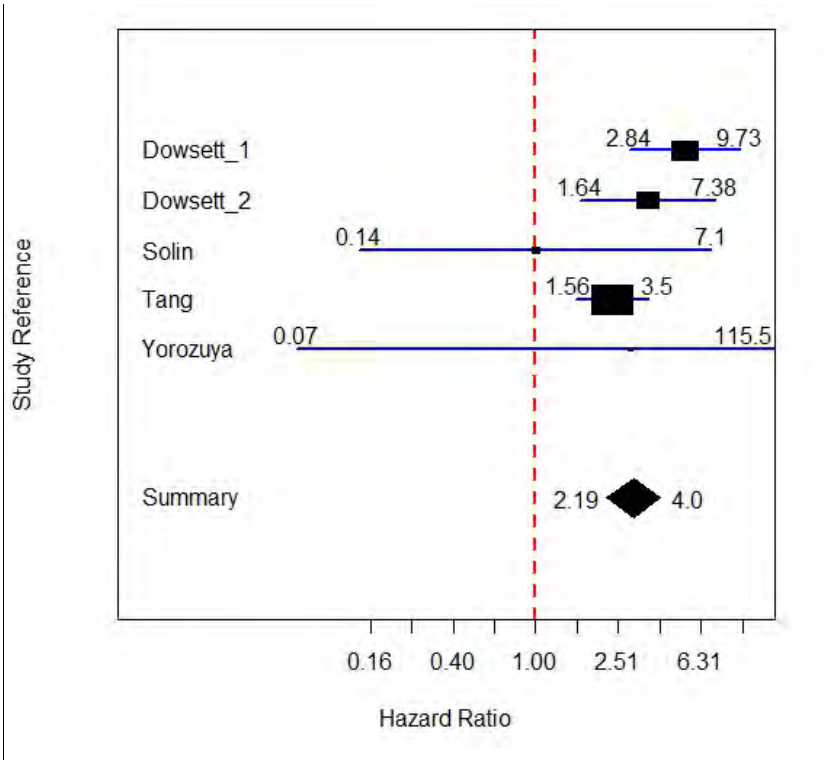
[a] Calculated from years by abstractor

Abbreviations: CI = confidence interval; cm = centimeter; ER = estrogen receptor; HR = hazard ratio; LRR = loco-regional recurrence; N+ = number positive; N0 = node negative; NR = not reported; OR = odds ratio; p = probability; PgR =progesterone receptor; RI = risk index; RI-PCT = risk index percentile; RS = risk score; RS-PCT = risk score percentile; vs. = versus.

Mamounas[72] and Solin[75] reported that the RS was not a significant predictor of the risk of LRR. Paik and Tang used the same set of patients but fitted different models to assess the prognostic value of the Oncotype DX RS in predicting distant recurrence. Models reported in Paik[74] and Tang[76] found statistically significant HRs between 2.3 and 3.1. Dowsett[70] reported a significant HR for both node-negative (5.25) and node-positive patients (3.47). The case-control study reported that cases having a distant recurrence had a higher RS than age-matched controls with no distant metastasis.

In a fixed effects model, our meta-analysis found an overall HR for RR for the high RS group compared with the intermediate/low RS group of 2.97 (95% CI, 2.19 to 4.0) (Figure 6).

Figure 6. Prognostic value of Oncotype DX Breast for risk of recurrence, meta-analysis of adjusted hazard ratios



Oncotype DX: Cancer-Specific Survival

We found two included studies rated as low RoB that reported on the prognostic value for CSS. One was a cohort study, Tang,[76] that included 668 patients, and one was a case-control study, Habel,[71] that included 566 patients. Tang[76] fit several models to the data and reported HRs ranging from 2 to 2.45, depending on the prognostic variables controlled for. Habel[71] reported that both tamoxifen-treated and tamoxifen-untreated breast cancer patients who died had higher RSs than matched patients who survived (Table 13).

Table 13. Breast cancer: Oncotype DX cancer-specific survival

Author, Year, Design, Number of Patients, Risk of Bias	Adjusted Risk (95% CI), p-value	p-value	What Variables Were Used in the Multivariate Model?
Habel, 2006[71] Case-control 566 Low	RS: Tamoxifen treated RR: 5.3 (1.6 to 17.2) p=0.003 Tamoxifen untreated RR: 2.4 (1.1 to 5.2) p=0.03	NR	Tumor size continuous (cm); grade (well, moderate, poor); RS (continuous)
Tang, 2011[76] Cohort 668 Low	RS-PCT/50 Model 4: HR: 2.45 (1.66 to 3.61) p<0.001 Model 5: HR: 2.02 (1.35 to 3.00) p<0001 Model 6: HR: 2.01 (1.35 to 2.98) p<0.001	NR	Model 4: Adjuvant! Online score (RI) as a composite covariate representing common prognostic factors but did not also include those factors individually Model 5: included Adjuvant! Online score (RI); also included common prognostic factors as individual covariates including age (>50 vs. ≤50); tumor size (cm); grade (moderate vs. well); grade (poor vs. well); RI-PCT/50 Model 6: included only individual prognostic factors as covariates including age (>50 vs. ≤50), tumor size (cm), grade (moderate vs. well), grade (poor vs. well), RI-PCT/50

[a] calculated from years by abstractor

Abbreviations: cm = centimeter; HR = hazard ratio; p = probability; RI = risk index; RI-PCT = risk index percentile; RR = relative risk; RS = risk score; RS-PCT = risk score percentile.

One cohort study, Tang,[76] rated as low RoB, was available. Tang fitted models with different combinations of adjustments for traditional prognostic factors. The HRs were of a similar magnitude in all three models, and the association between high RS and earlier death from all causes was positive and significant (Table 14).

Table 14. Breast cancer: Oncotype DX—overall survival

Author, Year, Design, N, Risk of Bias	Median Length of Followup to Determine Recurrence/Survival	Adjusted Ratio (95% CI), p-values	Variables Used in Multivariate Model
Tang, 2011[76] Cohort N=688 Low	14.3 years (range: NR)	RS-PCT/50 Model 4: HR: 1.77 (1.35 to 2.33) p<0.001 Model 5: HR: 1.65 (1.24 to 2.19) p<0.001 Model 6: HR: 1.65 (1.24 to 2.19) p<0.001	Model 4: Adjuvant! Online score (RI) as a composite covariate representing common prognostic factors but did not also include those factors individually Model 5: included Adjuvant! Online score (RI); also included common prognostic factors as individual covariates including age (>50 vs.≤50), tumor size (cm), grade (moderate vs. well), grade (poor vs. well), RI-PCT/50 Model 6: included only individual prognostic factors as covariates including: age (>50 vs.≤50), tumor size (cm), grade (moderate vs. well), grade (poor vs. well), RI-PCT/50

Abbreviations: CI = confidence interval; HR = hazard ratio; p = probability; NR = not reported; RI = risk index; RI-PCT = risk index percentile; RS = risk score; RS-PCT = risk score percentile.

Lung Cancer: *EGFR* and *KRAS* Mutations

Characteristics of Included Studies Assessing the Clinical Validity of *EGFR* Mutation Testing

We found 12 studies[78-89] that examined the added prognostic value of *EGFR* mutations in patients with nonsmall cell lung carcinoma (NSCLC). All were cohort studies. Sample sizes ranged from 50 to 524 patients. Median followup was not reported in all studies. Followup varied from 4 to 14 years. Studies were conducted in Japan, South Korea, Taiwan, China, various European countries, and the United States.

All studies primarily compared outcomes of patients with *EGFR* wild-type to those with *EGFR* mutations. A few looked at specific mutations such as the exon 19 deletion or the exon 21 L858R. The representation of female patients in the studies ranged from a low of 16 percent to a high of 65 percent. Race or ethnicity was reported only in two studies[84,89] conducted in the United States and Canada; Mak[84] and Tsao[89] had samples with 93 percent and 44 percent white patients, respectively.

Populations represented in the studies varied somewhat. The differences were both in cancer stage and cancer type. Four studies included all four stages,[78-80,88] three included stages I to III,[82,83,86] two included only stage I,[81,85] and the remaining included stages I and II. Not all studies specify the type of tumors included (Table 15).

Table 15. Characteristics of included studies: *EGFR mutation testing for lung* cancer

Author, Year Study Type Risk of Bias	N Length of Followup	Country(ies)	Disease Stage(s) Other Tumor/Disease Characteristics	Study groups	Race Ethnicity	Overall Age (years) % Female
An, 2012[78] Cohort Medium	524	China	I–IV		NR NR	Mean (range)=59.3 (23 to 88) 31%
Hiramitsu, 2010[79] Cohort High	193 470.4 weeks	Japan	I–IV Primary lung cancer	*EGFR*-WT *EGFR*-MUT	NR NR	Mean=63 50.3%
Kim, 2008[80] Cohort Medium	71 Mean (SD): 25.3 (11.1) months Range: 2.9 to 47.5 months	Republic of Korea (South Korea)	I–IV	*EGFR*-WT *EGFR*-MUT	NR NR	Median (range)=59.6 (38 to 85) 59.2%
Kim,2013[88] Cohort Medium	863 23.6 ± 0.7 months	Korea	I–IV	*EGFR*-MUT	NR	Mean=63 (27 to 87) 40%
Kobayashi, 2008[81] Cohort Medium	127 Median (range): 67 (12 to 134) months	Japan	IA Adenocarcinoma of the lung ≤20 mm diameter	*EGFR*-WT *EGFR*-MUT	NR NR	Median (range)=65 (38 to 83) 54.3%
Koh, 2010[82] Cohort High	136 Median: 491.3 weeks	Korea	IA–IIB	*EGFR*-WT *EGFR*-MUT	NR NR	Median (range)=61 (33 to 80) 26%
Liu, 2010[83] Cohort Medium	164 Range: 3.9 to 687 weeks	China (Taiwan)	I–IIIA Adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma	*EGFR*-WT *EGFR*-MUT	NR NR	NR 32.9%
Mak, 2011[84] Cohort Medium	123 Median (95% CI): 40.4 (30.5 to 52.6) months	United States	IIB–IIIB	*EGFR*-WT *EGFR*-MUT	White:93% Asian: 6% Other: 2% Ethnicity NR	Median (range)=62 (39 to 85) 65%
Matsumoto, 2006[85] Cohort Medium	107 Median (range) 63 (4 to 110) months	Japan	I	*EGFR*-WT *EGFR*-MUT	NR NR	NR 43%
Rouquette, 2012[86] Cohort Low	50 Median (interquartile range [IQR]): 35 (29 to 49) months	France	I–III Adenocarcinomas, squamous cell carcinomas, bronchioloalveolar carcinomas	*EGFR*-WT *EGFR*-MUT	NR NR	

Table 15. Characteristics of included studies: *EGFR mutation testing for lung* cancer (continued)

Author, Year Study Type Risk of Bias	N Length of Followup	Country(ies)	Disease Stage(s) Other Tumor/Disease Characteristics	Study groups	Race Ethnicity	Overall Age (years) % Female
Scoccianti, 2012[87] Cohort Medium	250 Up to 48 months	France, Germany, Ireland, Italy, the Netherlands, Poland, Spain, and the United Kingdom	T1–T4 Primary lung cancers	*EGFR*-WT *EGFR*-MUT	NR NR	NR 16%
Tsao, 2011[89] Cohort Low	436 NR	Canada and United States	IB–II	*EGFR*-WT *EGFR*-MUT	White=44.7% Other=6% Unknown=49%	NR *EGFR*-MUT: 13.4% *EGFR*-WT: 86.6%

Abbreviations: *EGFR* = gene name; IQR = interquartile range; mm = millimeter; MUT = mutation; N = number; NR = not reported; SD = standard deviation; WT = wild-type.

EGFR Mutation: Risk of Recurrence

Six cohort studies[80,81,84,87-89] (total N=1,870) assessed the prognostic value of this test for RR. Kobayashi[81] used recurrence as the outcome; Mak[84] looked at LRR and distant recurrence but provided adjusted results only for LRR. Scoccianti[87] used time to disease progression as the outcome. Tsao[89] used relapse-free survival as the outcome. Kim[80] used freedom from recurrence as the outcome. Three[80,81,89] of the five studies did not specify whether the outcome was loco–regional or distant or both.

Although the HRs for *EGFR* mutation suggest a protective effect (i.e., were all <1), none of the findings were statistically significant. Thus, the test for *EGFR* mutations does not appear to have prognostic value in predicting recurrence in NSCLC (Table 16).

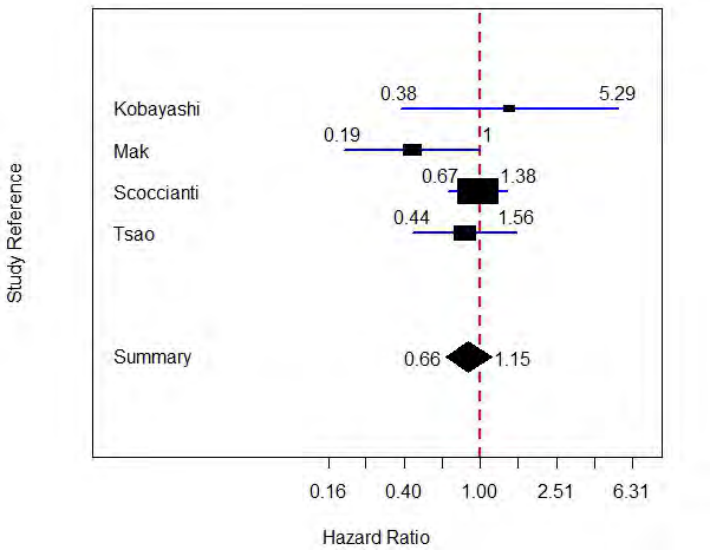
Table 16. Lung cancer: Risk of cancer recurrence/disease-free survival/recurrence-free survival for *EGFR*

Author, Year, Design, N, Risk of Bias	Adjusted Ratios, (95% CI) p-value Test Positive, Test Negative	Variables Used in Multivariate Model
Kim, 2008[80] Cohort 71 Medium	Freedom from Recurrence HR: NR, p=NS	Male, age >60 years, smoking+, BAC feature+, ≥Stage IIIA, *KRAS*+, EFGR−
Kim,2013[88] Cohort863 Medium	Freedom from recurrence EGFR NS	BAC, age, smoking, pathologic stage, cell type
Kobayashi, 2008[81] Cohort 127 Medium	Risk of cancer recurrence: HR: 1.42 (0.38 to 5.29) p=0.60 DFS: HR: 1.55 (0.54 to 4.49) p=0.42	Age (≥64 vs. <64); sex; smoking status (ever vs. never); CEA level (≥5.0 vs. <5.0); tumor size ≥15 vs. <15); non-BAC component (>50% v. ≤50%); *EGFR* mutation (yes or no)
Mak, 2011[84] Cohort 123 Medium	LRR HR: 0.44 (0.19 to 1.00) p=0.05	*EGFR* mutation status, stage, use of surgery, chemotherapy use, RT dose, primary tumor size
Soccianti, 2012[87] Cohort 250 Medium	Time to Disease Progression HR: 0.97 (0.67 to 1.38) p=0.68	Pathological tumor score, pathological node score
Tsao, 2011[89] Cohort 436 Low	RFS: HR: 0.83 (0.44 to 1.56) p=0.56	Sex, age, performance status, stage, histology, smoking status, baseline anemia, resection, serum LDH, p53 mutation status, and immunohistochemistry

Abbreviations: BAC = bronchioloalveolar cancer; CEA = carcinoembryonic antigen; CI = confidence interval; CISH = cytokine-inducible SH2-continaing protein; DFS = disease-free survival; *EGFR* = gene name; HR = hazard ratio; *KRAS* = gene name; LDH = lactate dehydrogenase; LRR = loco-regional recurrence; NR = not reported; NS = not statistically significant; p = probability; RFS = recurrence-free survival; RT = radiation therapy.

Using a fixed effects model, our meta-analysis, which included the four studies that reported HRs, found no added prognostic value for the *EGFR* mutation in predicting risk of recurrence HR: 0.87 95% CI (0.65 to 1.15) (Figure 7).

Figure 7. Prognostic value of *EGFR* mutation testing for risk of recurrence in lung cancer, meta-analysis of adjusted hazard ratios



EGFR Mutation: Cancer-Specific Survival

We found no studies meeting our inclusion criteria.

EGFR Mutation: Overall Survival

Six studies[81,83-85,88,89] representing 1,820 patients reported on the prognostic value of *EGFR* mutation for this outcome. One of the studies did not report any quantitative measures and therefore did not contribute to our strength of evidence determination. All studies looked at the prognostic value of the test in patients with NSCLC.

None of the included studies found a statistically significant HR for overall survival. The magnitude ranged from 0.6 to 1.6 in studies that reported quantitative measures. The other studies only reported that the result was not statistically significant (Table 17).

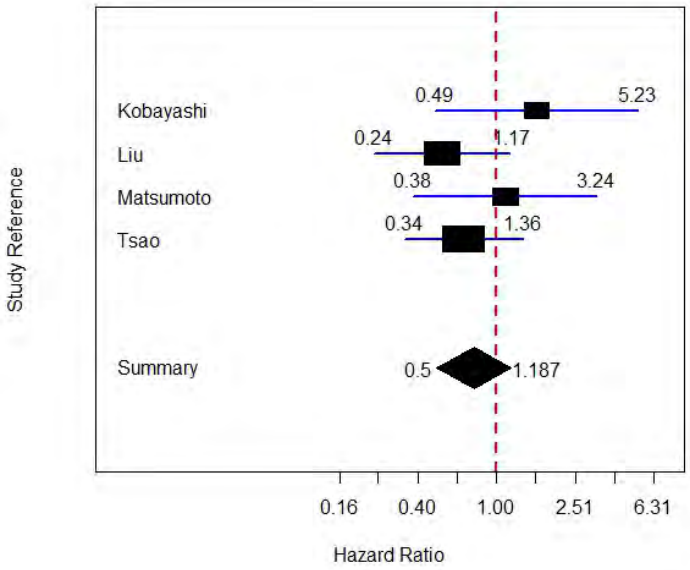
Table 17. Lung Cancer: *EGFR* mutation testing overall survival

Author, Year, Design, Risk of Bias	Adjusted Ratios, (95% CI) p-value Test Positive, Test Negative	Variables Used in Multivariate Model
Kim, 2013[88] Cohort 863 Medium	EGFR NR p=NS	BAC, Gender, age, pathologic stage, and smoking status
Kobayashi, 2008[81] Cohort 127 Medium	HR: 1.60 (0.49 to 5.23) p=0.44	Age (≥64 v. <64); sex; smoking status (ever vs. never); CEA level (≥5.0 vs. <5.0); tumor size (≥15 vs. <15); non-BAC component (>50% vs. ≤50%); *EGFR* mutation (yes or no)
Liu, 2010[83] Cohort 164 Medium	HR: 0.53 (95% CI, 0.24 to 1.17), p=NR	Year group, gender, age, pathology, stage, smoking status, CISH, *KRAS* mutation status, *EGFR* mutation expression
Mak, 2011[84] Cohort 123 Medium	HR: NR p=NS	*EGFR* mutation status, age, stage, PS score, smoking status, use of surgery, chemotherapy use, RT dose, primary tumor size (i.e., all outcomes that were significantly different between groups)
Matsumoto, 2006[85] Cohort 107 Medium	HR: 1.11 (0.38 to 3.24) p=0.85	Adjusted by all potential prognostic factors including gender, age, smoking status, tumor stage, tumor size, differentiation, *KRAS* status
Tsao, 2011[89] Cohort 436 Low	HR: 0.68 (0.34 to 1.36) p=0.28	Sex, age, performance status, stage, histology, smoking status, baseline anemia, type of resection, serum lactate dehydrogenase, p53 mutation status, and p53 immunohistochemistry

Abbreviations: BAC = bronchioloalveolar cancer; CI = confidence interval; CISH = cytokine-inducible SH2-continaing protein; *EGFR* = gene name; HR = hazard ratio; *KRAS* = gene name; NR = not reported; NS = not statistically significant; OS = overall survival; p = probability; PS = performance status; RT = radiation therapy.

Using a fixed effects model, our meta-analysis, which included the four studies that reported HRs, found no added prognostic value for the *EGFR* mutation in predicting overall survival HR, 0.77; 95% CI (0.50 to 1.19) (Figure 8).

Figure 8. Prognostic value of *EGFR* mutation testing for overall survival in lung cancer, meta-analysis of adjusted hazard ratios



Characteristics of Included Studies Assessing the Clinical Validity of *KRAS* Mutation testing

We found six studies[79,80,83,86,87,90] that examined the added prognostic value of *KRAS* mutations on the RR, CSS, and OS in patients with NSCLC. All were cohort studies with sample sizes that ranged from 100 to 250 patients. Studies were conducted in Japan, South Korea, Taiwan, and various European countries. Race/ethnicity was not reported in any of the studies. All studies compared outcomes of patients with *KRAS* wild-type with those with *KRAS* mutations. The representation of female patients in the studies ranged from a low of 16 percent to a high of 59 percent. Median length of follow-up was not available in all studies. Length of follow-up ranged from 4 to 14 years.

Populations represented in the studies varied somewhat. The differences were both in cancer stage and cancer type. Three studies included all stages.[79,80,87] Two included stages I to III,[83,86] and one[90] included only stage I (Table 18).

Table 18. Characteristics of included studies: *KRAS* mutation testing for nonsmall cell lung cancer

Author, Year Study Type Risk of Bias	N Length of followup	Country(ies)	Disease Stage(s) Other Tumor/ Disease Characteristics	Study Groups	Race Ethnicity	Overall Age (years) % Female
Guan, 2012[91] Cohort Medium	182 Median (all groups): 22.0 months Median (KRAS/WT): 22.7/20.6 months	China	I–IV Primary lung cancer	KRAS-WT KRAS-MUT	NR	Median: 59 37%
Hiramitsu, 2010[79] Cohort High	193 Median: 295.1 week	Japan	I–IV Primary lung cancer	*KRAS*-WT *KRAS*-MUT	NR	Mean=63 50.3%*
Kim, 2008[80] Cohort Medium	71 Mean (SD): 25.3 (11.1) months Range: 2.9 to 47.5 months	Republic of Korea (South Korea)	I–IV	*KRAS*-WT *KRAS*-MUT	NR	Median (range)=59.6 (38–85) 59.2%
Liu, 2010[83] Cohort Medium	164 Range: 3.9 to 687 weeks	China (Taiwan)	I–IIIA Adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma	*KRAS*-WT *KRAS*-MUT	NR	NR 32.9%
Rouquette, 2012[86] Cohort Low	100 Median (IQR): 35 (29 to 49) months	France	I–III Adenocarcinomas, squamous cell carcinomas, bronchioloalveolar carcinomas	*KRAS*-WT *KRAS*-MUT	NR	NR 50%
Scoccianti, 2012[87] Cohort Medium	250 Up to 48 months	France, Germany, Ireland, Italy, the Netherlands, Poland, Spain, and the United Kingdom	T1–T4 Primary lung cancers	*KRAS*-WT *KRAS*-MUT	NR	NR 16%
Woo, 2009[90] Cohort Medium	190 Median (range): 35.9 (1.1 to 82.5) months	Japan	IA–IB	*KRAS*-WT *KRAS*-MUT	NR	Mean (SD) (range)=67.8 (8.4) (45–85) 48.4%

Abbreviations: IQR = interquartile range; *KRAS* = gene name; MUT = mutation; N = number; NR = not reported; SD = standard deviation; WT = wild-type.

KRAS Mutation: Risk of Recurrence

Four studies[80,86,87,90] examining five cohorts(total N=611) rated as low or medium RoB assessed the prognostic value for RR (Table 19). Kim[80] and Scoccianti[87] studied

NSCLC, whereas Woo[90] studied the effect of the mutation specifically on stage I adenocarcinomas.

Table 19. Lung cancer: *KRAS* risk of cancer recurrence/disease-free survival/recurrence-free survival

Author, Year, Design, N, Risk of Bias	Adjusted Ratios, (95% CI) p-value Test Positive, Test Negative	Variables Used in Multivariate Model
Kim, 2008[80] Cohort 71 Medium	Freedom from recurrence HR: 2.8 (1.060 to 7.391) p=0.038	Multifactors chosen by step-forward method: male; age >60 years; smoking+; BAC feature+; ≥ Stage IIIA; *KRAS*+; *EGFR*−
Rouquette, 2012[86] Cohort 100 Low	DFS HR: NR, p=NS	*EGFR* mutation status, *KRAS* mutation status, HER2 expression, progesterone receptor expression, presence of lymphatic embols, tumor stage III
Scoccianti, 2012[87] Cohort 250 Medium	Time to Progression HR: 1.19 (0.75 to1.90) p=0.46	Pathological tumor score; pathological node
Woo, 2009[90] Cohort 1A N = 131 Cohort 1B N = 59 Medium	DFS For stage IA: HR: 4.55, (1.61 to 12.82) p=0.004 For Stage IB: HR: 14.99 (1.55–145.21) p=0.019	Age, tumor size, vessel invasion, Ki-67 expression

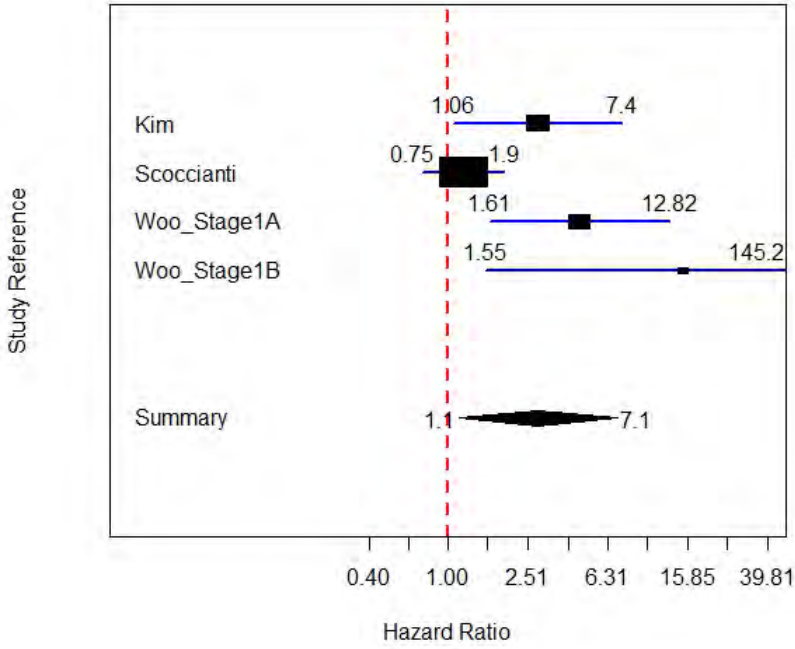
Abbreviations: BAC = bronchioloalveolar cancer; CI = confidence interval; CISH = cytokine-inducible SH2-containing protein; *EGFR* = gene name; HER2 = Human Epidermal Growth Factor Receptor 2, also known as Neu; HR = hazard ratio; *KRAS* = gene name; NR = not reported; OR = odds ratio; p = probability.

Kim[80] used freedom from recurrence as the outcome; the publication did not specify whether the recurrence was restricted to loco-regional or distant recurrence. Scoccianti[87] used time to disease progression as the outcome. Woo[90] also used disease-free recurrence as the outcome and did not specify if this was restricted to loco-regional or distant recurrence. Rouquette[86] used disease-free survival as the outcome and defined it as relapse, metastases, or death by any cause, whichever occurred first.

Rouquette[86] and Scoccianti[87] reported that *KRAS* mutation did not have added prognostic value. However, Kim[80] and Woo[90] reported that *KRAS* is a significant predictor for RR after controlling for other prognostic factors; the HRs range between 2.8 and 4.55.

Using a random effects model, our meta-analysis found added prognostic value of *KRAS* for risk of recurrence (HR, 2.84; 95% CI, 1.14 to 7.10) (Figure 9).

Figure 9. Prognostic value of *KRAS* mutation testing for risk of recurrence in lung cancer, meta-analysis of adjusted hazard ratios



KRAS Mutation: Cancer-Specific Survival

We found no studies meeting our inclusion criteria.

KRAS Mutation: Overall Survival

Two studies[80,91] with 253 patients reported that *KRAS* testing had added prognostic value for OS (Table 20).

Table 20. Lung cancer: *KRAS* overall survival

Author, Year, Design, N, Risk of Bias	Adjusted Ratios, (95% CI) p-value Test Positive, Test Negative	Variables Used in Multivariate Model
Kim, 2008[80] Cohort 71 Medium	*KRAS*+ HR: 3.339 (1.027 to10.862) p=0.045 *KRAS*+ 7.0%[a] (N=5) *KRAS*− 93.0%[a] (N=66)	Multifactors chosen by step-forward method: male; age >60 years; smoking+; BAC feature+; ≥ Stage IIIA; *KRAS*+
Guan, 2012[91] Cohort 182 Medium	KRAS(wild/mutation) (N=91/ N=91) HR: 2.69, 95 % CI 1.91–3.80; P< 0.001	Gender, age, KRAS/EGFR mutation status, pathology, TNM stage, PS, comorbidities, and smoking status

[a] calculated by abstractor

Abbreviations: BAC = bronchioloalveolar cancer; CI = confidence interval; HR = hazard ratio; *KRAS* = gene name; N = number; OR = odds ratio; p = probability.

Colorectal Cancer—*BRAF* Mutation

Characteristics of Included Studies Assessing the Clinical Validity of *BRAF* Mutation Testing

We included 17 studies[92-108] that examined the added prognostic value of *BRAF* mutations for RR, CSS, and OS in patients with CRC. All were cohort studies. Sample sizes ranged from 69 to 1,680. Median followup ranged from 3 to 8 years. Studies were conducted in Australia, China, various European countries, and the United States.

All studies compared outcomes of patients with *BRAF* wild-type to those with *BRAF* V600 mutations. The representation of female patients in the studies ranged from 2 percent to 53.6 percent. Race or ethnicity was not reported in most studies; one reported enrolling 98 percent white patients.[102]

Populations represented in the studies varied somewhat. The differences were both in cancer stage and the inclusion or exclusion of rectal cancers. Two studies[92,109] examined a sample of stage I and stage III colon cancers. Nine[93,94,99,102-106,108] included all stages and colon and rectal cancers. Two[95,102] included all stages of colon (not rectal) cancers. In the rest, one study[96] included both colon and rectal cancers stages I through III, another[97] had only stage III colon cancer patients, one study[98] included patients with only proximal colon cancer stages I through IV, and two[100,107] included stages II and III colon cancer (Table 21).

Table 21. Characteristics of included studies: *BRAF* mutation testing for colorectal cancer

Author, Year Study Type Risk of Bias	N Length of Followup	Country(ies)	Disease Stage(s) Other Tumor/ Disease Characteristics	Study Groups	Race Ethnicity	Overall Age (years) % Female
Eklof, 2013[108] Cohort Medium	197 (NSHDS) 414 (CRUMS) Median (CRUMS): 113 months Median (NSHDS): 102 months	Sweden	I–IV	*BRAF*-MUT *BRAF*-WT	NR	NR 43.7% (CRUMS) 56.9% (NSHDS)
Farina-Sarasqueta, 2010[92] Cohort Low	364 Stage II median (range): 239.1 (0 to 473.9) weeks Stage III median (range): 200 (8.7 to 578.3) weeks	The Netherlands	II–III	*BRAF*-WT *BRAF*-MUT	NR NR	Stage II mean age: 71.5 Stage III mean age: 62.5 45.6%
Kakar, 2008[93] Cohort High	69 NR	United States	I–IV	*BRAF*-WT *BRAF*-MUT	NR NR	NR 41%
Kalady, 2012[94] Cohort Medium	475 NR	United States	I–IV	*BRAF*-WT *BRAF*-MUT	NR NR	NR *BRAF*-WT: 85% *BRAF*-MUT: 15%
Liou, 2011[95] Cohort Medium	314 Median (range) 57 (49 to 82) months	China	I–IV	*BRAF*-WT *BRAF*-MUT	NR NR	Median WT 66 Median MUT 75 39%

Table 21. Characteristics of included studies: *BRAF* mutation testing for colorectal cancer (continued)

Author, Year Study Type Risk of Bias	N Length of Followup	Country(ies)	Disease Stage(s) Other Tumor/ Disease Characteristics	Study Groups	Race Ethnicity	Overall Age (years) % Female
Lochhead, 2013[105] Cohort Medium	1253 Median: 8.2 years, range(3.5–13.1)years	United States	I-IV	*BRAF*-WT BRAF-MUT	NR	Mean age +/− SD 68.5 ±8.7 55%:
Maestro, 2007[96] Cohort Medium	324 Median (IQR): 43 (27 to 63) months	Spain	Duke's Stages A–D	*BRAF*-WT *BRAF*-MUT	NR NR	Mean (range): 69.6 (30 to 95) 47.9%
Ogino, 2012[97] Cohort Medium	506 Median: 91.2 months	United States	III	*BRAF*-WT *BRAF*-MUT	NR NR	Median (SD): 59.7 (11.5) 46%
Pai, 2012[98] Cohort High	181 Median (range): 52 (0 to 331) weeks	United States	I–IV	*KRAS*-MUT *BRAF*-MUT *KRAS* and *BRAF*-WT	NR NR	Mean (range): 67 (33 to 98) 47%
Phipps, 2012[99] Cohort Medium	1980 Median (range): 7.4 (0.4 to 13.8) years	United States	Stages categorized according to SEER conventions (localized, regional, distant, or unknown)	*BRAF*-WT *BRAF*-MUT	NR NR	NR 54.5%
Roth, 2010[100] Cohort Medium	1307 Median: 296 weeks	Switzerland, Belgium, Italy, Hungary, Spain, France, and United Kingdom	II–III	*BRAF*-WT *BRAF*-MUT	NR NR	NR 42.2%
Roth, 2012[107] Cohort Medium	1404 Median: 69 months	Switzerland	II-III	*BRAF*-MUT *BRAF*-WT	NR	Median (range): 60 (21-76) 42.8%
Samadder, 2013[106] Cohort Medium	563 NR	United States	I-IV	*MSS* *MSI-L/H* *BRAF*-MUT *BRAF*-WT	NR	Mean (SD): 73.9 (5.92) 100%
Samowitz, 2005[101] Cohort High	803 NR	United States	I–IV	*BRAF*-WT (microsatellite stable tumors) *BRAF*-MUT (V600E) (microsatellite stable tumors)	NR NR	Range: 30 to 79 45.8%
Shaukat, 2010[102] Cohort Medium	194 NR	United States	I–IV	*BRAF*-WT *BRAF*-MUT	White: 98% NR	NR 2%

Table 21. Characteristics of included studies: *BRAF* mutation testing for colorectal cancer (continued)

Author, Year Study Type Risk of Bias	N Length of Followup	Country(ies)	Disease Stage(s) Other Tumor/ Disease Characteristics	Study Groups	Race Ethnicity	Overall Age (years) % Female
Tie, 2011[103] Cohort Medium	525 38.5 months (median recurrence) 12.9 months (median overall survival)	Australia	I–IV	*BRAF*-WT *BRAF*-MUT	NR NR	Median 70.5 50%
Zlobec, 2010[104] Cohort Medium	404 Median: 234.8 weeks (all patients) Median: 260.9 weeks (CSS)	Switzerland	T1–T4	*BRAF*-WT *BRAF*-MUT	NR NR	Mean (range): 69.5 (40–95) 53.6%

Abbreviations: *BRAF* = gene name; CSS = cancer-specific survival; IQR = interquartile range; *KRAS* = gene name; MUT = mutation; NR = not reported; SD = standard deviation; SEER = Surveillance, Epidemiology, and End Results; WT = wild-type.

BRAF: Risk of Recurrence

Five cohort studies[92,97,100,103,107] rated as low or medium RoB (total N=4,106) examined the prognostic significance of the *BRAF* mutation for RR (Table 22). The definitions for the outcomes differed a little between the studies. Farina[92] defined disease-free survival (DFS) as time to recurrence of disease or distant metastasis; Ogino[97] defined DFS as time to disease recurrence or distant metastasis or death from any cause; Roth (2010),[100] Roth (2012)[107] and Tie[103] defined their outcome as recurrence of CRC and did not specify if recurrence includes local and distant.

Table 22. Colorectal cancer: *BRAF* risk of cancer recurrence/disease-free survival/recurrence-free survival

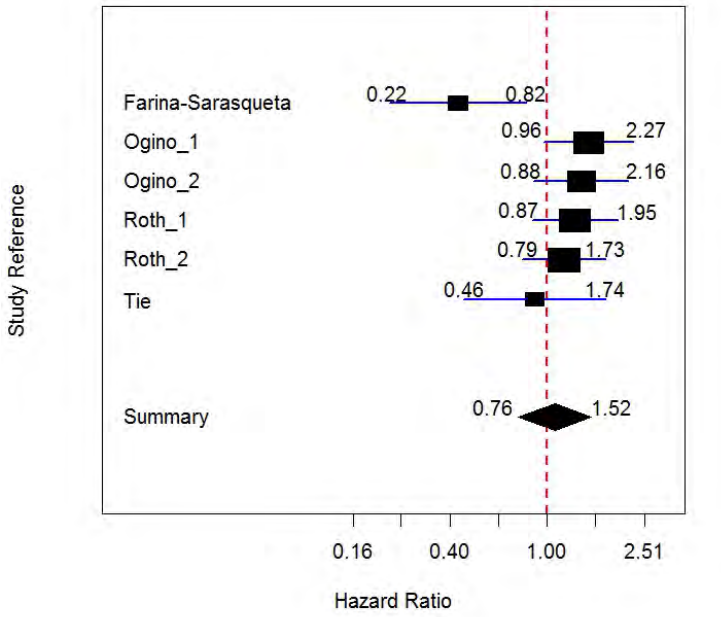
Author, Year, Design, N Test (Cancer), Risk of Bias	Adjusted Ratios, (95% CI) p-value	Variables Used in Multivariate Model
Farina-Sarasqueta, 2010[92] Cohort 364 Low	DFS HR=0.43 (0.22 to 0.82) p=NR	Differentiation grade, age, sex, tumor location, tumor stage, node stage, *KRAS* status, *BRAF* status, and MSI status
Ogino, 2012[97] Cohort 506 Medium	DFS HR: 1.48 (0.96 to 2.27) p=NR RFS HR: 1.38 (0.88 to 2.16) p=NR	Age, sex, baseline body mass index (BMI), family history of CRC in first-degree relatives, performance status, presence or absence of perforation and/or obstruction at surgery, treatment arm, tumor location, tumor and node stage, *KRAS* status, MSI status
Roth, 2010[100] Cohort 1307 Medium	RFS, All subjects HR: 1.30 (0.87 to 1.95) p=0.21 Stage II subjects HR: 1.93 (0.67 to 5.60) p=0.23 Stage III subjects HR: 1.23 (0.79 to 1.92) p=0.35	Treatment arm, age, sex, grade, tumor site, nodal stage, MSI, *KRAS*, *BRAF* mutation status
Roth, 2012[107] Cohort 1404 Medium	RFS, HR: 1.17 (0.79 to 1.73) p=0.44	Age, sex, grade, stage, number of examined lymph nodes, site, treatment group, MSI status, SMAD4 expression, 18qLOH status, and KRAS
Tie, 2011[103] Cohort 525 Medium	RR HR: 0.89 (0.46 to 1.74) p=0.74	Age, gender, stage, tumor site, use of adjuvant therapy

Abbreviations: BMI = body mass index; *BRAF* = gene name; CI = confidence interval; CRC = colorectal cancer; DFS = disease-free survival; HR = hazard ratio; *KRAS* = gene name; MSI = microsatellite instability; N = number; NR = not reported; p = probability; RFS = recurrence-free survival; RR = risk of recurrence.

The included studies reported on the prognostic value of testing for *BRAF* after controlling for certain traditional prognostic factors such as stage, sex, and age. Three of the four studies found no association between *BRAF* and prognosis in adjusted analyses. Farina[92] reported a significant association (HR, 2.32; 95% CI, 1.21 to 4.54) between RR and the *BRAF* mutation.

Using a random effects model, our meta-analysis found no added prognostic value of *BRAF* for risk of recurrence (HR, 1.07; 95% CI, 0.76 to 1.52) (Figure 10).

Figure 10. Prognostic value of *BRAF* mutation testing for risk of recurrence in colorectal cancer, meta-analysis of adjusted hazard ratios



BRAF for Colorectal Cancer: Cancer-Specific Mortality

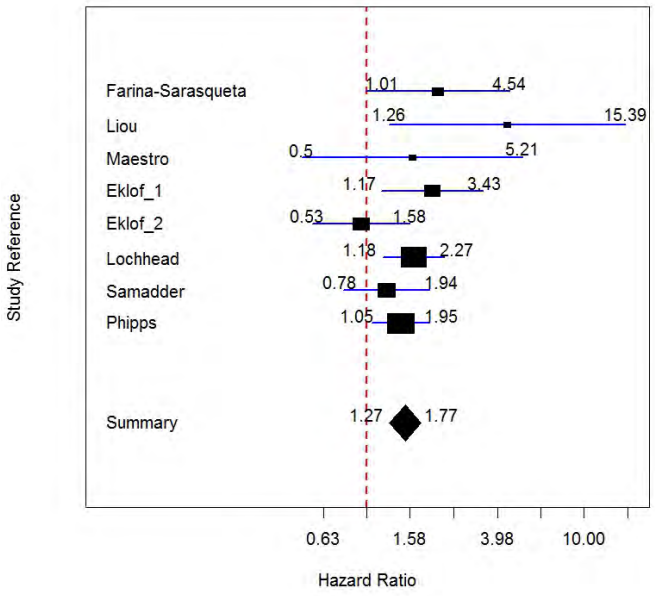
Seven studies reporting on eight different cohorts with low or medium RoB (total N=5,409) reported on *BRAF* mutation and CSS.[92,95,96,99,105,106,108] Five out of seven cohorts had statistically significant HRs, suggesting a positive association between mutation and greater risk of cancer-specific death (Table 23). A summary measure was estimated using a fixed effects model. The overall HR for CSS for the patients with wild-type compared with mutated was 1.50, 95% CI (1.26 to 1.77) (Figure 11).

Table 23. Colorectal cancer: *BRAF* cancer-specific mortality

Author, Year, Design, Risk of Bias	Adjusted Ratios, (95% CI) p-value	Variables Used in Multivariate Model
Farina-Sarasqueta, 2010[92] Cohort 364 Low	HR: 2.12 (1.01 to 4.54) p=0.05	Differentiation grade, age, sex, tumor location, tumor stage, node stage, *KRAS* status, *BRAF* status, and MSI status
Eklof, 2013[108] Cohort 197 (NSHDS) 414 (CRUMS) Medium	(NSDHS, N = 196) HR: 1.998 (1.165 to 3.426) p=NR (CRUMS, N = 377) HR: 0.94 (0.529 to1.576) p=NR	Sex, age at diagnosis, stage, tumor site
Liou, 2011[95] Cohort 314 Medium	HR: 4.41 (1.26 to 15.39) p=0.02	Age, sex, stage, lymphatic invasion, venous invasion, tumor differentiation, CEA level (>5 vs. ≤5 ng/mL)
Lochhead, 2012[105] Cohort 1,253 Medium	*BRAF*-MUT HR:1.64 (1.18 to 2.27) p =0.003	Age at diagnosis, year of diagnosis, BMI, differentiation grade LINE-1 methylation, stage, KRAS and P1K3CA status
Maestro, 2007[96] Cohort 324 Medium	HR: 1.62 (0.50 to 5.21) p=0.38	Age, sex, Duke's stage, tumor site, differentiation grade, histology, adjuvant chemotherapy, MSI, and *BRAF*
Phipps, 2012[99] Cohort 1980 Medium	HR: 1.43 (1.05 to 1.95) p=NR	Age at diagnosis, sex, time from diagnosis to enrollment, SEER stage, MSI status
Samadder, 2013[106] Cohort 563 Medium	HR: 1.23 (0.78 to 1.94) p=0.38	Age at diagnosis, anatomic subsite, tumor grade, SEER stage, chemotherapy exposure, and radiation therapy exposure

Abbreviations: *BRAF* = gene name; CEA = carcinoembryonic antigen; CI = confidence interval; HR = hazard ratio; *KRAS* = gene name; MSI = microsatellite instability; ng/mL = nanograms/milliliter; NR = not reported; p = probability; SEER = Surveillance, Epidemiology, and End Results.

Figure 11. Prognostic value of *BRAF* mutation testing for cancer-specific survival in colorectal cancer, meta-analysis of adjusted hazard ratios



BRAF for Colorectal Cancer: Overall Survival

Eleven studies with twelve cohorts rated as low or medium RoB reported on prognostic value of *BRAF* for OS in patients with CRC[92,94,95,97,99,100,102,103,105-107] (total N=7,610) (Table 24).

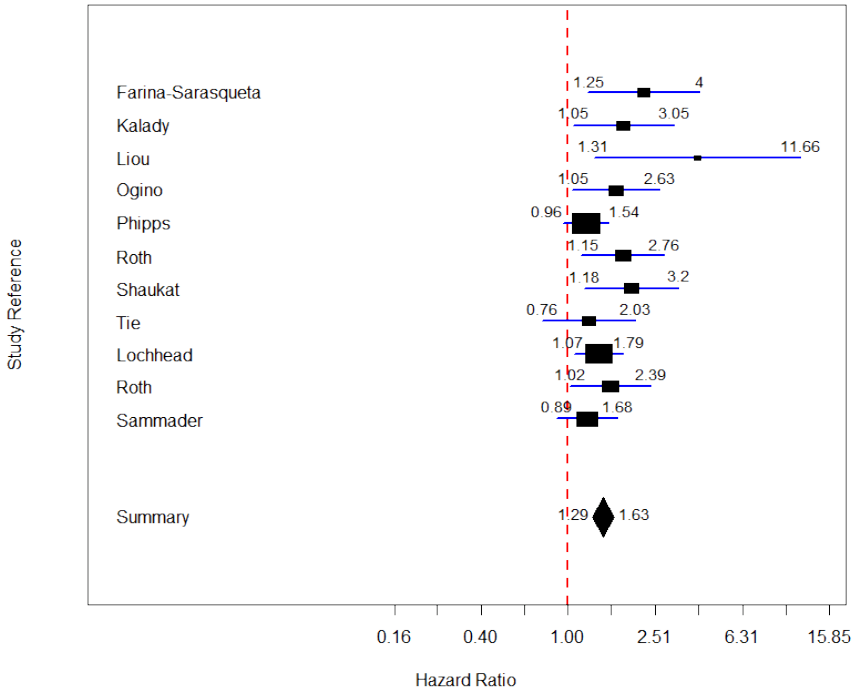
Nine out of twelve cohorts reported significant associations between *BRAF* mutation status and survival. The summary HR for overall survival used a fixed effects model for patients with wild-type compared with those with *BRAF* mutations of 1.45 (1.3 to 1.62) (Figure 12).

Table 24. Colorectal cancer: *BRAF* overall survival

Author, Year, Design, Risk of Bias	Adjusted Ratios, (95% CI) p-value	Variables Used in Multivariate Model
Farina-Sarasqueta, 2010[92] Cohort 364 Low	*BRAF* HR: 2.22 (1.25 to 4) p<0.05	Differentiation grade, age, sex, tumor location, tumor stage, node stage, *KRAS* status, *BRAF* status, and MSI status
Kalady, 2012[94] Cohort 475 Medium	HR: 1.79 (1.05 to 3.05) p=0.031	*BRAF* mutation, MSI status, TNM stage, sex, age (>55 years), differentiation, proximal tumor site
Liou, 2011[95] Cohort 314 Medium	HR: 3.91 (1.31 to 11.66) p=0.014	Age, sex, stage, lymphatic invasion, venous invasion, tumor differentiation, CEA level (>5 vs. ≤5 ng/mL)
Lochhead, 2012[105] Cohort 1,253 Medium	*BRAF*-Mut HR: 1.38 (1.07-1.79) p = 0.013	Age at diagnosis, Year of diagnosis, BMI, differentiation grade LINE-1 methylation, stage, KRAS and P1K3CA status
Ogino, 2012[97] Cohort 506 Medium	HR: 1.66 (1.05 to 2.63) p=NR	Age, sex, baseline BMI, family history of CRC in first-degree relatives, performance status, presence or absence of perforation and/or obstruction at surgery, treatment arm, tumor location, T and N stage, *KRAS* status, MSI status
Phipps, 2012[99] Cohort 1980 Medium	HR: 1.21 (0.96 to1.54) p=NR	Age at diagnosis, sex, time from diagnosis to enrollment, SEER stage, MSI status
Roth, 2010[100] Cohort 1307 Medium	All subjects HR: 1.78 (1.15 to 2.76) p=0.010 Stage II subjects: HR: 3.83 (1.09 to 13.5) p=0.036 Stage III subjects: HR: 1.67 (1.04 to 2.68) p=0.035	Treatment arm, age, sex, grade, tumor site, nodal stage, MSI, *KRAS*, *BRAF* mutation status
Roth, 2012[107] Cohort 1404 Medium	HR: 1.56 (1.02 to 2.39) p=0.04	Age, sex, grade, stage, number of examined lymph nodes, site, treatment group, MSI status, SMAD4 expression, 18qLOH status, and KRAS
Samadder, 2013[106] Cohort 563 Medium	HR: 1.22 (0.89 to 1.68) p=0.21	Age at diagnosis, anatomic subsite, tumor grade, SEER stage, chemotherapy exposure, and radiation therapy exposure
Shaukat, 2010[102] Cohort 194 Medium	HR: 1.95 (1.18 to 3.20) p=0.008	Age, tumor grade, TNM (tumor-node-metastasis) stage, and MSI status
Tie, 2011[103] Cohort 503 Medium	*BRAF* mutant for Stages I–III HR: 1.24 (0.76 to 2.03) p=0.40	Age, gender, stage, tumor site, use of adjuvant therapy

Abbreviations: BMI = body mass index; *BRAF*= gene name; CEA = carcinoembryonic antigen; CI = confidence interval; HR= hazard ratio; *KRAS* = gene name; MSI = microsatellite instability; NR = not reported; p = probability; SEER = Surveillance, Epidemiology, and End Results; TNM= tumor, node, metastases.

Figure 12. Prognostic value of *BRAF* mutation testing for overall survival in colorectal cancer, meta-analysis of adjusted hazard ratios



Colorectal Cancer: *KRAS* Mutation

Characteristics of Included Studies Assessing the Clinical Validity of *KRAS* Mutation Testing

The genetic test for *KRAS* mutations described here checks for mutations in codons 12 and 13 in the *KRAS* gene. We included 14 cohort studies[92,95,98,100,103,106-114] that examined the effect of *KRAS* mutations on the RR, CSS, or OS in patients with CRC (Table 25). Sample sizes ranged from 135 to 1,404. Median followup was between 3 to 12 years. Studies were conducted in Australia, China, various European countries, and the United States.

Table 25. Characteristics of included studies: *KRAS* mutation testing for colorectal cancer

Author, Year Study Type Risk of Bias	N Length of Followup	Country(ies)	Disease Stage(s) Other Tumor/ Disease Characteristics	Study Groups	Race Ethnicity	Overall Age (years) % Female
Bazan, 2005[109] Cohort Medium	160 Median (range): 71 (34 to 115) months	Italy	Duke's stages A–D	*KRAS*-WT *KRAS*-MUT	NR NR	Median (range): 66 (31 to 88) 52.5%
Deschoolmeester, 2010[110] Cohort Unclear	164 Median: 242 weeks (overall survival): Median: 232 weeks (disease-free survival)	Belgium	I–IV	*KRAS*-WT *KRAS*-MUT	NR NR	Median: 65 +/− 13 48.8%
Eklof, 2013[108] Cohort Medium	197 (NSHDS) 414 (CRUMS) Median (CRUMS): 113 months Median (NSHDS): 102 months	Sweden	I-IV	*KRAS*-MUT *KRAS*-WT	NR	NR 43.7% (CRUMS) 56.9% (NSHDS)
Farina-Sarasqueta, 2010[92] Cohort Low	364 Stage II median (range): 239.1 (0–473.9) weeks Stage III median (range): 200 (8.7–578.3) weeks	The Netherlands	II–III	*KRAS*-WT *KRAS*-MUT	NR NR	Stage II mean age: 71.5 Stage III mean age: 62.5 45.6%
Geido, 2002[111] Cohort Low	135 Mean (range): 72 (3 to103) months	Italy	Duke's Stages A–D Sporadic CRC: proximal (i.e., cecum, ascending and transverse colon sites) and distal (i.e., descending and sigmoid colon and rectum)	*KRAS*-WT *KRAS*-MUT *KRAS*-MUT (G-->A) *KRAS*-MUT (G-->C/T)	NR NR	Median: 67 44%
Imamura, 2012[112] Cohort High	1075 Median (IQR): 611 (433 to 840) weeks	United States	I–IV	*KRAS*-WT *KRAS*-MUT codon 12 *KRAS*-MUT codon 13	NR NR	Mean (SD): 68.5 (8.7) 55%

Table 25. Characteristics of included studies: *KRAS* mutation testing for colorectal cancer (continued)

Author, Year Study Type Risk of Bias	N Length of Followup	Country(ies)	Disease Stage(s) Other Tumor/ Disease Characteristics	Study Groups	Race Ethnicity	Overall Age (years) % Female
Li, 2012[114] Cohort Medium	78 Max FU was 43 months; Min was 12	China	I-IV	KRAS-WT KRAS-MUT	NR	Overall NR: Range: 28-70y 44.9% overall KRAS-WT:74.3% KRAS-MUT:25.7%
Liou, 2011[95] Cohort Medium	314 Median (range) 57 (49–82) months	China	I–IV	*KRAS*-WT *KRAS*-MUT	NR NR	*KRAS*-WT mean (SD): 64.8 (12.7) *KRAS*-MUT mean (SD): 65.7 (13.1) *KRAS*-WT: 42.6% *KRAS*-MUT: 57%
Ogino, 2009[113]; Cohort Medium	508 Median: 323.6 weeks	United States	III	*KRAS*-WT *KRAS*-MUT	NR NR	Median (SD): 59.8 (11.5) 46%
Pai, 2012[98] Cohort High	181 Median (range): 12 (0 to 76) months	United States	I–IV	*KRAS*-MUT *KRAS* WT	NR NR	Mean (range): 67 (33 to 98) 47%
Roth, 2012[107] Cohort Medium	1404 Median: 69 months	Switzerland	II-III	*KRAS*-MUT *KRAS*-WT	NR	Median (range): 60 (21-76) 42.8%
Roth, 2010[100] Cohort Medium	1,299 Median: 296 weeks	Switzerland, Belgium, Italy, Hungary, Spain, France, and United Kingdom	II–III	*KRAS*-WT *KRAS*-MUT	NR NR	NR 42.3%
Samadder, 2013[106] Cohort Medium	563 NR	United States	I-IV	*KRAS*-MUT *KRAS*-WT	NR	Mean (SD) [age at diagnosis]: 73.9 (5.92) 100%

Table 25. Characteristics of included studies: *KRAS* mutation testing for colorectal cancer (continued)

Author, Year Study Type Risk of Bias	N Length of Followup	Country(ies)	Disease Stage(s) Other Tumor/ Disease Characteristics	Study Groups	Race Ethnicity	Overall Age (years) % Female
Tie, 2011[103] Cohort Medium	510 Median 38.5 months (recurrence) Median 12.9 months (overall survival)	Australia	I–IV	*KRAS*-WT *KRAS*-MUT	NR	*KRAS*-WT median: 70.7 *KRAS*-MUT median: 70.4 *KRAS*-WT: 68% *KRAS*-MUT: 32%

Abbreviations: IQR = interquartile range; *KRAS* = gene name; MUT = mutation; N = number; NR = not reported; SD = standard deviation; WT = wild-type.

All studies compared outcomes of patients with *KRAS* wild-type with those who had *KRAS* mutations. Some also looked at mutations in codon 13 and the mutation from G to C/t and G to A. The representation of female patients in the studies ranged from 42 percent to 55 percent. Race or ethnicity was not reported in any of the studies.

Populations represented in the studies varied somewhat. The differences were both in cancer stage and the inclusion or exclusion of rectal cancers. Five studies[103,107-112,114] included all stages and colon and rectal cancers. Among the rest, one[95] included all stages of colon (not rectal) cancers, another[92] examined a sample of stage II and stage III colon cancers, and Maestro[96] included stages I to III and both colon and rectal cancers. Ogino[97] had only stage three colon cancer patients, Pai[98] studied proximal colon stages I through IV, and Roth[100] included stage II and III colon cancer.

KRAS for Colorectal Cancer: Risk of Recurrence

Five cohort studies (total N=4,085) rated as low or medium RoB[92,100,103,107,113] examined RR as an outcome (Table 26). Farina[92] defined DFS as time to recurrence of disease or distant metastasis; Ogino[113] defined DFS as time to disease recurrence or distant metastasis or death from any cause; Roth[100] did not define their outcome of relapse-free survival but presumably included loco-regional and distant recurrence; and Tie[103] defined their outcome as recurrence of CRC, which presumably means loco-regional and distant recurrence.

Table 26. Colorectal cancer: *KRAS* risk of cancer recurrence/disease-free survival/recurrence-free survival

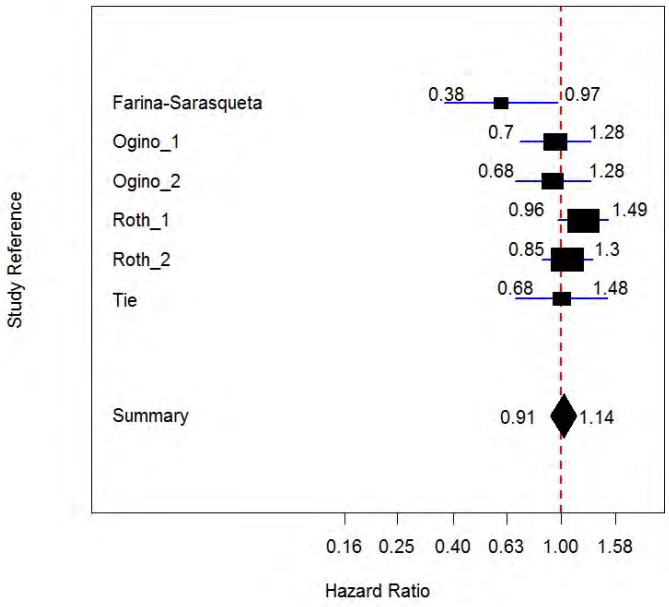
Author, Year, Design, N, Test (Cancer), Risk of Bias	Adjusted Ratios, (95% CI) p-value	Variables Used in Multivariate Model
Farina-Sarasqueta, 2010[92] Cohort 364 Low	DFS HR: 0.6 (0.38 to 0.97) p=NR	Differentiation grade, age, sex, tumor location, tumor stage, node stage, *KRAS* status, *BRAF* status, and MSI status
Ogino, 2009[113] Cohort 508 Medium	DFS: HR: 0.95 (0.70 to 1.28) p=NR RFS: HR: 0.93 (0.68 to 1.28) p=NR	Age, sex, BMI, tumor location, tumor and node stage, presence or absence of perforation and/or obstruction at diagnosis, performance status, MSI status, and treatment arm
Roth, 2010[100] Cohort 1,299 Medium	RFS All subjects HR:1.20 (0.96 to 1.49) p=0.11 Stage II subjects HR: 1.26 (0.75 to 2.13) p=0.38 Stage III subjects HR: 1.21 (0.95 to 1.54) p=0.12	Treatment arm, age, sex, grade, tumor site, nodal stage, MSI, *KRAS*, *BRAF* mutation status
Roth, 2012[107] Cohort 1404 Medium	RFS HR: 1.05 (0.85 to 1.30) p=0.65	Age, sex, grade, stage, number of examined lymph nodes, site, treatment group, MSI status, SMAD4 expression, 18qLOH status, and BRAF
Tie, 2011[103] Cohort 510 Medium	RR HR: 1.00 (0.68 to 1.48) p=1.00	Age, gender, tumor site, stage

Abbreviations: BMI = body mass index; *BRAF* = gene name; CI = confidence interval; DFS = disease-free survival; HR = hazard ratio; *KRAS* = gene name; MSI = microsatellite instability; N = number; p = probability; RFS = recurrence-free survival.

The included studies reported on the prognostic value of testing for *KRAS* after controlling for certain traditional prognostic factors such as stage, sex, and age. Three out of the four studies reported no statistically significant association between *KRAS* and prognosis in adjusted analyses. Farina reported a significant association between the *KRAS* wild-type and improved survival.

Our meta-analysis found no significant added prognostic value of *KRAS* mutation testing for RR in patients with CRC HR, 1.02 (95% CI, 0.91 to 1.14) (Figure 13).

Figure 13. Prognostic value of *KRAS* mutation testing for risk of recurrence in colorectal cancer, meta–analysis of adjusted hazard ratios



KRAS for Colorectal Cancer: Cancer-Specific Mortality

We found two studies (N = 1,174) that looked at the prognostic effect of KRAS mutation on CSS. Eklof[108] examined the effect of KRAS on two different populations; the Colorectal Cancer in Umea Study (CRUMS) and the Northern Sweden Health Disease Study (NSHDS). They report a significant HR in CRUMS and a nonsignificant HR in the NHSDS. Sammader reports a nonsignificant HR (Table 27).

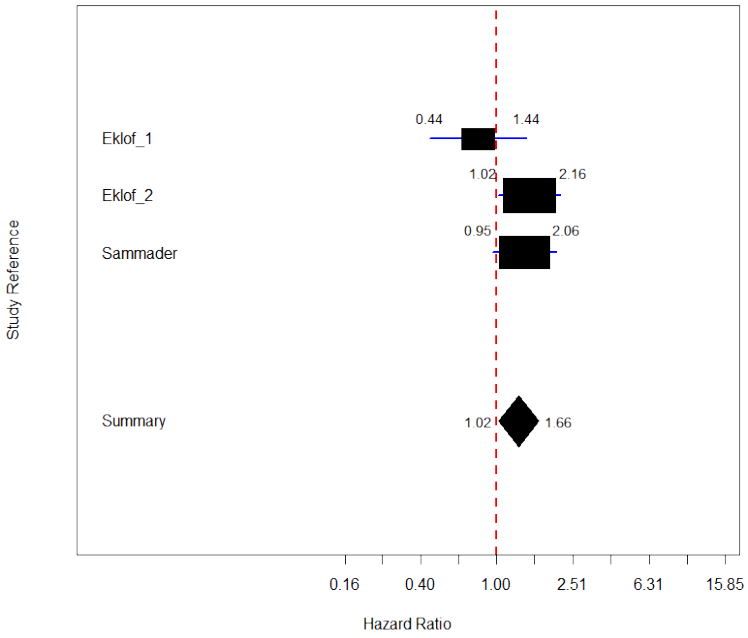
Our meta-analysis found that KRAS mutation has a significant prognostic effect on CSS with a HR of 1.30 (95% CI, 1.02 to 1.66) (Figure 14).

Table 27. Colorectal cancer: *KRAS* cancer-specific survival

Author, Year, Design, Risk of Bias	Adjusted Ratios, (95% CI) p-value	Variables Used in Multivariate Model
Eklof, 2013[108] Cohort 197 (NSHDS) 414 (CRUMS) Medium	(NSDHS, N = 179) HR: 0.798 (0.443 to1.438) p=NR (CRUMS, N = 378) HR: 1.485 (1.023 to 2.15 Colorectal Cancer in Umeå Study (CRUMS)5) p=NR	Sex, age at diagnosis, stage, tumor site
Samadder, 2013[106] Cohort 563 Medium	HR: 1.40 (0.95 to 2.06) p=.08	Age at diagnosis, anatomic subsite, tumor grade, SEER stage, chemotherapy exposure, and radiation therapy exposure

Abbreviations: CRUMS = Colorectal Cancer in Umea Study; HR = hazard ratio; *KRAS* = gene name; N = number; p = probability. NSHDS= Northern Sweden Health Disease Study

Figure 14. Prognostic value of *KRAS* mutation testing for CSS in colorectal cancer, meta–analysis of adjusted hazard ratios



KRAS for Colorectal Cancer: Overall Survival

Ten cohort studies with low or medium RoB[92,95,100,103,106,107,109,111,113,114] (total N=5,328) examined overall survival as an outcome (Table 28). The included studies reported on the prognostic value of testing for *KRAS* after controlling for certain traditional prognostic factors such as stage, sex, and age. Six out of seven studies reported no statistically significant association between *KRAS* mutation status and OS in adjusted analyses. Bazan and Geido[109,111] reported significant associations between *KRAS* gene mutation status and survival.

Our meta-analysis found no significant added prognostic value of *KRAS* mutation testing for OS in patients with CRC HR: 1.22 (0.95, 1.55) (Figure 15).

Table 28. Colorectal cancer: *KRAS* overall survival

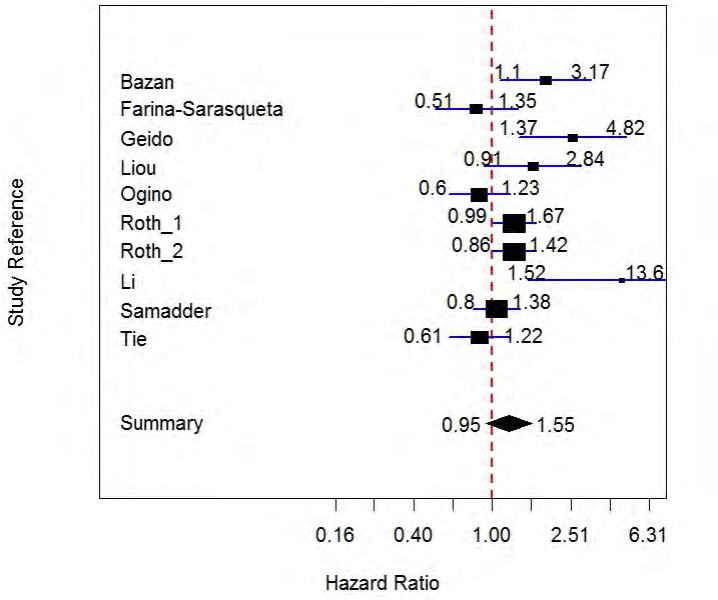
Author, Year, Design, Risk of Bias	Adjusted Ratios, (95% CI) p-value	Variables Used in Multivariate Model
Bazan, 2005[109] Cohort MSI (colorectal) Medium	HR: 1.86 (1.10 to 3.17) p<0.05	Duke's stage, surgical resection, DNA-aneuploidy, high SPF
Farina-Sarasqueta, 2010[92] Cohort 364 Low	HR = 0.83(0.51 to 1.35) p=NR	Differentiation grade, age, sex, tumor location, T stage, nodal stage, *KRAS* status, *BRAF* status, and MSI status
Geido, 2002[111] Cohort 135 Low	Overall RR: 2.57 (1.37 to 4.82) p=0.003 G-A transition mutation subtype RR: 2.29 (1.12 to 4.66) p=0.02 G-C/T transversion mutation subtype RR: 3.34 (1.34 to 8.36) p=0.009	Model #1 (used to calculate RR of overall *KRAS* mutation): age, site, Duke's stages B and C, DNA ploidy, wild-type vs. mutated *KRAS*-2 status Model #2 (used to calculate RRs of G-->A and G-->C/T *KRAS* mutations): Same as Model #1, but with *KRAS* mutations subdivided into two specific types named above
Li, 2012[114] Cohort 78 Medium	KRAS mutation RR: 4.552 (1.522 -13.610) p=0.007	Sex, KRAS mutation, age, growth pattern, location of tumor, tumor differentiation, lymph node metastasis, liver metastasis, TNM stage
Liou, 2011[95] Cohort 314 Medium	HR: 1.61 (0.91 to 2.84) p=0.101	Age, sex, stage, use of adjuvant chemotherapy
Ogino, 2009[113] Cohort 508 Medium	HR: 0.86 (0.60 to 1.23) p=NR	Age, sex, BMI, tumor location, tumor and node stage, presence or absence of perforation and/or obstruction at diagnosis, performance status, MSI status, and treatment arm
Roth, 2010[100] Cohort 1,299 Medium	All subjects: HR: 1.29 (0.99 to 1.67) p=0.060 Stage II subjects: HR: 1.51 (0.79 to 2.90) p=0.21 Stage III subjects: HR:1.28 (0.97 to 1.71) p=0.086	Treatment arm, age, sex, grade, tumor site, nodal stage, MSI, *KRAS*, *BRAF* mutation status

Table 28. Colorectal cancer: *KRAS* overall survival (continued)

Author, Year, Design, Risk of Bias	Adjusted Ratios, (95% CI) p-value	Variables Used in Multivariate Model
Roth, 2012[107] Cohort 1,404 Medium	HR: 1.10 (0.86 to 1.42) p=0.45	Age, sex, grade, stage, number of examined lymph nodes, site, treatment group, MSI status, SMAD4 expression, 18qLOH status, and BRAF
Samadder, 2013[106] Cohort 563 Medium	HR: 1.05 (0.80 to 1.38) p=0.70	Age at diagnosis, anatomic subsite, tumor grade, SEER stage, chemotherapy exposure, and radiation therapy exposure
Tie, 2011[103] Cohort 503 Medium	HR: 0.86 (0.61 to1.22) p=NR	Age, gender, tumor site, stage

Abbreviations: BMI = body mass index; *BRAF* = gene name; CI = confidence interval; DNA = deoxyribonucleic acid; HR = hazard ratio; *KRAS* = gene name; MSI = microsatellite instability; NR = not reported; RR = relative risk; SPF = S-phase Fraction.

Figure 15. Prognostic value of *KRAS* mutation testing for overall survival in colorectal cancer, meta–analysis of adjusted hazard ratios



Colorectal Cancer: Microsatellite Instability (MSI)

Characteristics of Included Studies Assessing the Clinical Validity of MSI

The test for MSI described here uses the five reference microsatellite markers D5S345, D2S123, BAT25, BAT26, and D17S250 (Bethesda markers) to establish microsatellite instability. We included 17 cohort studies[96,103-107,115-125] that examined the added prognostic value of MSI for RR, CSS, or OS in patients with CRC (Table 29). Sample sizes ranged from 55 to 1,175. Median follow up ranged from 3 to 14 years. Studies were conducted in Australia, China, various European countries, Taiwan, and the United States.

Table 29. Characteristics of included studies: MSI for colorectal cancer

Author, Year Study Type Risk of Bias	N Length of Followup	Country(ies)	Disease Stage(s) Other Tumor/ Disease Characteristics	Study Groups	Race Ethnicity	Overall Age (years) % Female
Chang, 2006[115] Cohort Medium	213 Median (range): 208.8 (17.4 to 334.8) weeks	China (Taiwan)	I–IV	MSI-H MSS	NR NR	Median (range): 67.6 (23 to 86)
Donada, 2011[116] Cohort Low	55 Median: 396.72 weeks, 25th–75th percentile=193.1 weeks to 443.5 weeks	Italy	II–III	MSI-H Non-MSI-H	NR NR	Mean (SD) (range): 62.9 (9.1) (35 to 79)
Guibodoni, 2001[117] Cohort Medium	109 Median Recurrence: 74 (50 to 120) months Overall survival: 78 (46 to 120) months	Italy	II–III	MSI-H MSS/MSI-L	NR NR	NR 58.7%
Gyrfe, 2000[118] Cohort Medium	587 Mean (SD): 7.2 (0.1) years	United States	T1–T4	MSI MSS	NR NR	Mean (SD): 43.1 (0.3) 50%
Hong, 2012[119] Cohort Medium	1,125 Median: 42 months	South Korea	I–IV	MSI MSS	NR NR	Median (range): 61 (25 to 92) 3.6%
Jensen, 2009[120] Cohort Medium	311 Median (range): 6.1 (4.1 to 11.3) years	Denmark	II–IV	MSI MSS	NR NR	NR 48.8%
Kim, 2007[121] Cohort Low	542 Censored at 5 years	United States	Duke's Stages B or C	MSI-H MSS/MSI-L	NR NR	NR NR
Lin, 2012[122] Cohort Medium	709 Median (range): 204.9 (4 to 796) weeks	China	I–III	MSI-H MSS/MSI-L	NR NR	Mean (SD): 68.8 (11.5) 32.4%

Table 29. Characteristics of included studies: MSI for colorectal cancer (continued)

Author, Year Study Type Risk of Bias	N Length of Followup	Country(ies)	Disease Stage(s) Other Tumor/ Disease Characteristics	Study Groups	Race Ethnicity	Overall Age (years) % Female
Lochhead, 2012[105] Cohort Medium	1,253 Median:8.2 years, range(3.5-13.1)years	United States	I-IV	MSI-H MSS	NR NR	NR NR
Maestro, 2007[96] Cohort Medium	324 Median (IQR): 43 (27-63) months	Spain	Duke's Stages A–D	MSS MSI-L MSI-H	NR NR	Mean (range): 69.6 (30 to 95)
Roth, 2012[107] Cohort Medium	1,404 Median: 69 months	Switzerland	II-III	MSI-H MS-L/S	NR	Median (range): 60 (21-76) 42.8%
Samadder, 2013[106] Cohort Medium	563 Mean(SD) 73.9 (5.92)	United States	Grade I-IV	MSS MSI-L MSI-H	NR NR NR	NR NR NR
Shia, 2008[123] Cohort High	130 Median (range): 98 (12 to 168) months	United States	I–IV	MSI-H Non-MSI-H	NR NR	Median (range): 65.5 (31 to 85) 47.7%
Soreide, 2009[124] Cohort Medium	186 Range: 291.45 to 495.9 weeks	Norway	I–III	MSS MSI-H	NR NR	Median (IQR): 67 (59 to 73)
Tie, 2011[103] Cohort Medium	503 Recurrence: 38.5 months Cancer specific survival: 12.9 months	Australia	I–IV	MSI MSS	NR NR	MSI median: 75.8 MSS median: 69.4 MSI: 15% MSS: 85%
Yoon, 2011[125] Cohort Low	2,028 43 (1 to 85) months	Korea	II–III	MSI-H MSI-L MSS	NR NR	Mean (SD): 56.7 (12) MSI-H: 10% MSI-L: NR MSS: 90%
Zlobec, 2010[104] Cohort Medium	404 Median: 234.8 weeks (all patients) Median: 260.9 weeks (cancer-specific survival)	Switzerland	T1–T4	MSI-H MSS/MSI-L	NR NR	Mean (range): 69.5 (40 to 95) 53.6%

Abbreviations: IQR = interquartile range; MSI = microsatellite instability; MSI-H = microsatellite instability high; MSS = microsatellite stability; N = number; NR = not reported; SD = standard deviation; WT = wild-type.

All studies compared outcomes of patients with MSI-H with those with MSS/MSI-L. The representation of female patients in the studies where sex is reported ranged from 3.6 percent to 53 percent. Race or ethnicity was not reported in any of the studies.

There were some differences in the populations examined in the different publications. The differences were with respect to stage and whether rectal cancers were included. Eight studies[103-106,115,118,119,123] included patients with colon and rectal cancer at all stages. Four studies[96,107,121,124] included patients with stage II or III colon or rectal cancers. Guidoboni[117] examined a sample of patients with stage I or II proximal colon cancer only; Jensen[120] included patients with stages II, III, and IV colon and rectal cancer; Lin[122] had a sample of only stage III colon cancer; and Yoon[125] included patients with colon and rectal cancer in stages I through III.

MSI for Colorectal Cancer: Risk of Recurrence

Ten cohort studies with low or medium RoB (total N=7,130)[103,107,115,117,119-122,124,125] examined RR as an outcome (Table 30). Several studies[103,115,117,122,125] had DFS or recurrence as an outcome but did not specify whether they were looking at loco-regional or distant recurrence. Hong[119] defined DFS as disease recurrence or progression; Jensen[120] looked at recurrence-free survival, which was defined as relapse of primary disease or death; Kim[121] had RFS as an outcome, which they defined as time to first occurrence of a tumor recurrence; and Soreido[124] looked at any recurrence and separately at loco-regional and distant metastasis.

Table 30. Colorectal cancer: MSI risk of recurrence

Author, Year, Design, N, Test (Cancer), Risk of Bias	Adjusted Ratios, (95% CI) p-value	Variables Used in Multivariate Model
Chang, 2006[115] Cohort 213 Medium	4 year DFS MSI-H vs. MSS HR: 0.49 (0.18 to 1.38) p=0.179	TNM stage, P53 mutation, CEA level, differentiation, MSI, location
Guidoboni, 2001[117] Cohort MSI (colorectal) 109 Medium	DFS HR: 0.32 (0.15 to 0.72) p=0.002	Sex, age as continuous, TNM stage
Hong, 2012[119] Cohort 1,125 Medium	DFS Overall HR: 0.57 (0.32 to 0.96) p=0.034 Colon HR: 0.61 (0.33 to 1.10) p=0.100 Rectum HR: 0.48 (0.12 to1.97) p=0.311	Stage, sex, age
Jensen, 2009[120] Cohort 311 Medium	RR HR: 0.3 (0.2 to 0.7) p=0.0007	Thymidylate synthase, dihydropyrimidine, gender, age, stage, differentiation, peripheral invasion, vascular invasion, perforation ileus

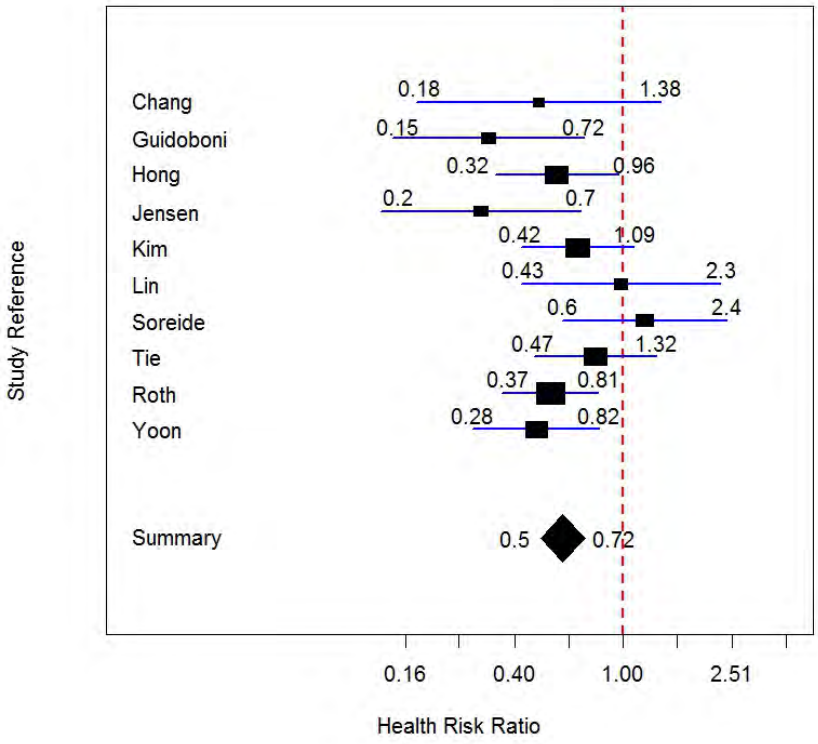
Table 30. Colorectal cancer: MSI risk of recurrence (continued)

Author, Year, Design, N, Test (Cancer), Risk of Bias	Adjusted Ratios, (95% CI) p-value	Variables Used in Multivariate Model
Kim, 2007[121] Cohort 542 Low	RR Overall: RR: 0.68 (0.42 to1.09) p=0.1 RR Untreated group: HR: 0.77 (0.40 to1.48) p=NR RR Treated group: HR: 0.60 (0.30 to 1.19) p=NR	Treatment and MSI/treatment interaction, age, sex, stage, tumor site
Lin, 2012[122] Cohort 709 Medium	DFS HR: 0.982 (0.425 to 2.268) p=0.965	Age, gender, stage, differentiation
Roth, 2012[107] Cohort 1404 Medium	RFS MSI-H vs. MS-L/S HR: 0.54 (0.37 to 0.81) p=0.003	Age, sex, grade, stage, number of examined lymph nodes, site, treatment group, SMAD4 expression, 18qLOH status, BRAF, and KRAS
Soreide, 2009[124] Cohort 186 Medium	LRR MSI adjusted for both age and sex OR: 2.5 (1.0 to 6.1) p=0.047 MSI adjusted for tumor location OR: 3.1 (1.1 to 8.8) p=0 .026 Any recurrence OR 1.2 (0.6 to 2.4) p=0.64	Age, sex, MSI and variables that had p-values <0.1 on univariate analysis
Tie, 2011[103] Cohort 503 Medium	DFS HR: 0.79 (0.47 to1.32) p=0.36	Age, gender, tumor site, stage
Yoon, 2011[125] Cohort 2,028 Low	DFS MSI-H: HR: 0.48 (0.28 to 0.82) p=0.007	Age, location, gender, CEA, node, distant metastases, histology, lympho-vascular invasion, growth type, adjuvant

Abbreviations: CEA = carcinoembryonic antigen; CI = confidence interval; DFS = disease-free survival; HR = hazard ratio; LRR = loco-regional recurrence; MSI = microsatellite instability; MSI-H = microsatellite instability high; MSI-L = microsatellite instability low; MSS = microsatellite stability; N = number; NR = not reported; OR = odds ratio; p = probability; RR = relative risk; TNM = tumor, node, metastases.

The included studies reported on the prognostic value of testing for MSI after controlling for certain traditional prognostic factors such as stage, sex, and age. All but two studies reported point estimates, suggesting an association between MSI-H and lower RR. Four out of nine studies reported statistically significant associations between MSI and RR in adjusted analyses—finding that MSI-H was associated with better prognosis. Our meta-analysis found a lower RR for the patients with MSI-H compared with those with MSS (HR, 0.60; 95% CI, 0.50 to 0.72) (Figure 16).

Figure 16. Prognostic value of microsatellite instability for risk of recurrence in colorectal cancer, meta-analysis of adjusted hazard ratios



MSI for Colorectal Cancer: Cancer-Specific Survival

Six cohort studies rated as medium RoB[96,104-106,122,124] (total N =3,439) reported on CSS as an outcome (Table 31).

Table 31. Colorectal cancer: MSI cancer-specific mortality

Author, Year, Design, N, Risk of Bias	Adjusted Ratios, (95% CI) p-value	Variables Used in Multivariate Model
Lin, 2012[122] Cohort 709 Medium	HR: 0.891 (0.363 to 2.183) p=0.8	Age, sex, stage, differentiation, MSI status
Lochhead, 2013[105] Cohort 1253 Medium	MSI-H vs. MSS HR: 0.28 (0.17-0.46) p<0.001	Age, year of diagnosis, BMI, tumor differentiation LINE-1 methylation),disease stage. KRAS and P1K3CA status
Maestro, 2007[96] Cohort 324 Medium	MSI-L vs. MSS HR: 0.72 (0.29 to 1.80) p=NR MSI-H vs. MSS HR: 0.33 (0.12 to 0.92) p=NR Any MSI vs. MSS: p=0.036	Age, sex, Duke's stage, tumor site, differentiation grade, histology, adjuvant chemotherapy, MSI, and *BRAF*

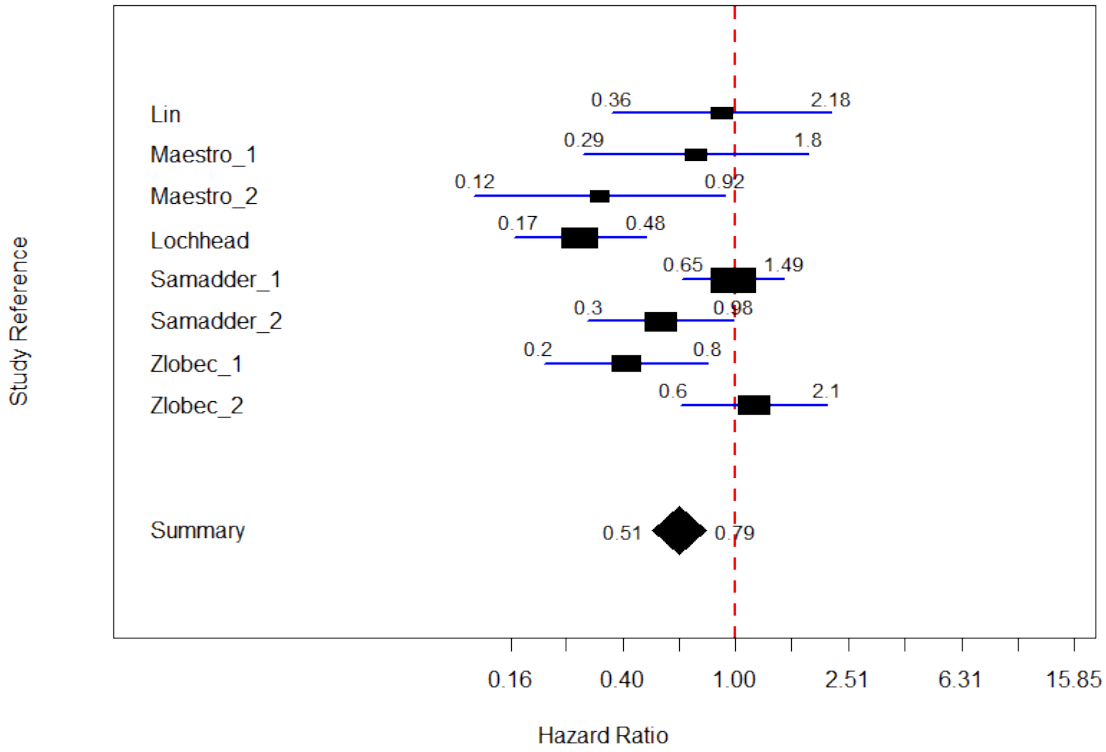
Table 31. Colorectal cancer: MSI cancer-specific mortality (continued)

Author, Year, Design, N, Risk of Bias	Adjusted Ratios, (95% CI) p-value	Variables Used in Multivariate Model
Samadder, 2013[106] 2013 Cohort 563 Medium	MSI –L HR: 0.98 (0.65-1.49) p=.08 MSI-H HR: 0.54 (0.30-0.98) p=.08	Age at diagnosis, anatomic subsite, tumor grade, SEER stage, chemotherapy exposure and radiation therapy exposure
Soreide, 2009[124] Cohort 186 Medium	HR: NR (NR) p=0.722	Age, sex, MSI status, and variables that had p-values <0.1 on univariate analysis
Zlobec, 2010[104] Cohort 404 Medium	Right-sided location MSI-H HR: 0.41 (0.2 to 0.8) p=0.015 Left-sided location MSI-H HR: 1.16 (0.6 to 2.1) p=0.622	pT stage, pN stage, vascular invasion and MSI in right- and left-sided CRC

Abbreviations: *BRAF* = gene name; CI = confidence interval; CRC = colorectal cancer; HR = hazard ratio; MSI = microsatellite instability; MSI-H = microsatellite instability high; MSI-L = microsatellite instability low; MSS = microsatellite stability; NR = not reported; p = probability; pN = pathological node score; pT = pathological tumor score.

The included studies reported on the prognostic value of testing for MSI after controlling for certain traditional prognostic factors such as stage, sex, and age. Two of the four studies reported a statistically significant association between MSI and prognosis of CSS in adjusted analyses. Zlobec[104] reported a positive association (HR 0.41 [0.2 to 0.8]) between MSI-H for right-sided tumors for CSS. Maestro[96] reported a significant HR association between MSI-H and CSS (HR 0.33 [0.12, 0.92]). Our meta-analysis found an overall HR for CSS for patients with MSI-H tumors compared with MSS tumors of 0.63; 95% CI, (0.51 to 0.79) (Figure 17).

Figure 17. Prognostic value of microsatellite instability for cancer specific survival in colorectal cancer, meta-analysis of adjusted hazard ratios



MSI for Colorectal Cancer: Overall Survival

Twelve cohort studies[103,105,107,115-122,125] (total N =8,839) rated as low or medium RoB examined overall survival (Table 32). Populations examined in the different publications varied somewhat.

The included studies reported on the prognostic value of testing for MSI after controlling for certain traditional prognostic factors such as stage, sex, and age. Four out of 10 studies reported a statistically significant association between MSI and prognosis for OS in adjusted analyses. All 4 found that MSI-H is a good prognostic marker for OS.

Our meta-analysis found an overall HR for OS for patients with MSI-H compared with MSS of 0.57; 95% CI (0.43 to 0.77) (Figure 18).

Table 32. Colorectal cancer: Overall survival with MSI

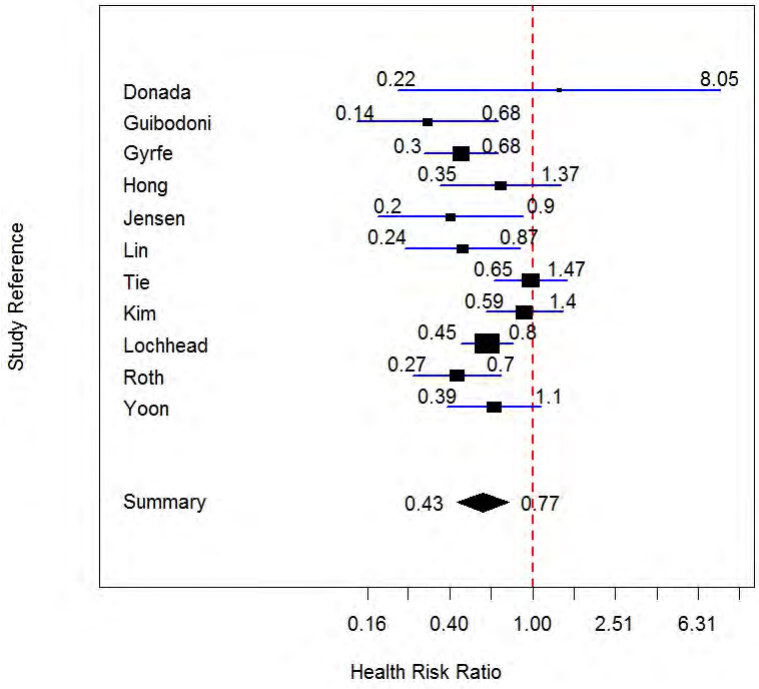
Author, Year, Design, N Risk of Bias	Adjusted Ratios, (95% CI) p-value	Variables Used in Multivariate Model
Chang, 2006[115] Cohort 213 Medium	4-year OS HR: NR MSI-H vs. MSS: p=0.858	TNM (I, II, III, IV), p53 mutation (yes vs. no), CEA level 2 (high vs. low), grade of differentiation (poor vs. well/moderate), MSI status (MSI-H vs. MSS), location (right, left, rectum)
Donada, 2011[116] Cohort 55 Low	MSI-H vs. non-MSI-H HR: 1.34 (0.22 to 8.05) p=0.75	Age, sex, tumor location (left-transverse-right), stage (III vs. II), grading (G3-G2-G1), TS expression (high vs. low), TP expression (high vs. low), DPD expression (high vs. low), MSI status (MSI-H vs. non-MSI-H)
Kim, 2007[121] Cohort 542 Low	MSI-H vs. MSS/MSI-L Stratified by treatment RR=0.91 (0.59, 1.4) Treated group HR=1.02 (0.56 to 1.85) Untreated group HR=0.82 (0.44 to 1.51)	Stratified by treatment: surgery alone vs. surgery + chemotherapy Age, sex, stage, tumor site
Guibodoni, 2001[117] Cohort 109 Medium	HR: 0.31 (0.14 to 0.68) p=NR	Sex, age, TNM stage
Gyrfe, 2000[118] Cohort 587 Medium	MSI vs. MSS HR: 0.45 (0.30 to 0.68) p<0.0001	Lymph-node metastases, microsatellite status (MSS, MSI); tumor invasion (T1-4); distant-organ metastases—microsatellite status (MSS, MSI); tumor invasion (T1–4)
Hong, 2012[119] Cohort 1125 Medium	Overall 0.7 (0.35 to 1.37) p=0.292 Colon 0.62 (0.29 to 1.4) Rectum 1.07 (0.26 to 1.4)	Stage, sex, age
Jensen, 2009[120] Cohort 311 Medium	HR: 0.4 (0.2 to 0.9) p=0.02	Microsatellite instability, thymidylate synthase , dihydropyrimidine dehydrogenase , sex, age, stage, differentiation, perineural invasion, vascular invasion, perforation, ileus
Lin, 2012[122] Cohort 709 Medium	HR: 0.459 (0.241 to 0.872) p=0.017	Age, sex, stage, differentiation (well to moderate vs. poor to undifferentiated), MSI status (MSI-H vs. MSI L/S)
Lochhead, 2013[105] Cohort 2,012 Medium	MSI-high vs. MSS HR: 0.60 (0.45-0.80) p<0.001	Age, year of diagnosis, BMI, tumor differentiation LINE-1 methylation, stage, KRAS and P1K3CA status
Roth, 2012[107] Cohort 1404 Medium	HR: 0.43 (0.27 to 0.70) p=0.001	Age, sex, grade, stage, number of examined lymph nodes, site, treatment group, SMAD4 expression, 18qLOH status, BRAF, and KRAS
Tie, 2011[103] Cohort 503 Medium	HR: 0.98 (0.65 to 1.47) p=0.92	Age, gender, tumor site, stage

Table 32. Colorectal cancer: Overall survival with MSI (continued)

Author, Year, Design, N Risk of Bias	Adjusted Ratios, (95% CI) p-value	Variables Used in Multivariate Model
Yoon, 2011[125] Cohort 2028 Low	HR: 0.65 (0.39 to1.10) p=0.11	Age, gender, location, MSI status, CEA, lymph node metastasis, distant metastasis, lymphovascular invasion, histology, adjuvant chemotherapy

Abbreviations: CEA = carcinoembryonic antigen; CI = confidence interval; DPD = dihydropyrimidine dehydrogenase; HR = hazard ratio; *KRAS* = gene name; MSI = microsatellite instability; MSI-H = microsatellite instability high; MSI-L = microsatellite instability low; MSI-L/S = microsatellite instability low or stable; MSS = microsatellite stability; N = number; p = probability; RR = relative risk; TNM = tumor, node, metastases; TP = thymidine phosphorylase; vs. = versus.

Figure 18. Prognostic value of microsatellite instability for overall survival in colorectal cancer, meta-analysis of adjusted hazard ratios



Colorectal Cancer: Oncotype DX

Characteristics of Included Studies Assessing the Clinical Validity of Oncotype DX Colon

We included one cohort study[126] that examined the added prognostic value of Oncotype DX Colon for RR, CSS, or OS in patients with CRC (Table 33).

Table 33. Characteristics of included studies: Oncotype DX for colorectal cancer

Author, Year Study Type Risk of Bias	N Length of Followup	Country(ies)	Disease Stage(s) Other Tumor/ Disease Characteristics	Study Groups	Race Ethnicity	Overall Age years) % Female
Venook 2013[126] Cohort Medium	690 NR	United States	II	Recurrent patients Nonrecurrent patients	White: 92% NR	NR 41.9%

Abbreviations: N = number; NR = not reported.

Oncotype DX: Risk of Recurrence

One included cohort study rated as medium RoB (N=690) reported this outcome.[126] The study examined a 12-gene RS as the outcome in stage II CRC patients who were part of the CALGB trial. All patients with recurrence and a random sample of patients with no recurrence were included in the study.

The study reported that the RS from Oncotype DX (treated as a continuous variable) was a significant predictor (HR 1.68; 95% CI, 1.18 to 2.39) after controlling for standard prognostic markers (Table 34).

Table 34. Colorectal cancer: Oncotype DX risk of cancer recurrence/disease-free survival/recurrence-free survival

Author, Year, Design, N, Test (Cancer), Risk of Bias	Adjusted Ratios, (95% CI) p-value	Variables Used in Multivariate Model
Venook 2013[126] Cohort 690 Medium	RS: HR: 68 (1.18 to 2.38) p=0.004	MMR, tumor state, number of nodes examined, grade , LVI, RS

Abbreviations: CI = confidence interval; HR = hazard ratio; LVI = lymphovascular invasion; MMR = mismatch repair; N = number; p = probability; RS = risk score.

Oncotype DX: Cancer-Specific Mortality

We found no studies meeting our inclusion criteria.

Oncotype DX: Overall Survival

We found no studies meeting our inclusion criteria.

Bladder Cancer: UroVysion

Characteristics of Included Studies Assessing the Clinical Validity of UroVysion

UroVysion is a fluorescence in situ hybridization (FISH) test of exfoliated urothelial cells that has been shown to be sensitive in terms of diagnosing urothelial cancer. It was designed as a diagnostic and not a prognostic test. In this report the test is being evaluated for its prognostic value with respect to predicting recurrence.

We included 3 studies[127-129] that examined the added prognostic value of UroVysion for RR, CSS, or OS in patients with bladder cancer (Table 35). Sample sizes ranged from 42 to 138. Studies were conducted in the United States and Switzerland. Race or ethnicity

was not reported in any of the studies. One study was rated as high RoB and was not included in our main data synthesis.[129]

Table 35. Characteristics of included studies: UroVysion for urinary bladder cancer

Author, Year Study Type Risk of Bias	N Length of Followup	Country(ies)	Disease Stage(s) Other Tumor/ Disease Characteristics	Study Groups	Race Ethnicity	Overall Age (years) % Female
Kamat, 2012[127] Cohort Low	126	United States	TA or T1 Nonmuscle invasive bladder cancer (primary or recurrent)	UroVysion+ UroVysion−	NR NR	Median: 67.5 24%
Whitson, 2009[128] Cohort Low	42 Median (range): 91.3 (21.7 to 230.5) weeks	United States	T1 High-risk superficial bladder tumor	UroVysion+ UroVysion−	NR NR	Median (range): 68 (41 to 97) NR
Zellweger, 2006[129] Cohort High	138 Median (range): 19.2 (4 to 52) months	Switzerland	Stage pTa to pT3; 9 tumors without information on stage were also included	UroVysion+ UroVysion−	NR NR	Median (range): 68.5 (33.4 to 92.5) 15.9%

Abbreviations = N = number; NR = not reported.

UroVysion: Risk of recurrence

Two cohort studies (total N = 168) reported on UroVysion and RR. Whitson[128] retrospectively studied patients who underwent intravesical therapy (IVT), and Kamat[127] prospectively enrolled patients who were scheduled to undergo IVT. Both studies reported that the test is a significant predictor after controlling for traditional prognostic factors (Table 36).

Table 36. Key Question 3: Bladder cancer: UroVysion risk of cancer recurrence/disease-free survival/recurrence-free survival

Author, Year, Design, N, Risk of Bias	Adjusted Ratio (95% CI), p-value	Variables Used in Multivariate Model
Kamat, 2012[127] Cohort 126 Low	HR: NR p<0.01	Stage, grade, history of prior tumors, concomitant CIS, use of postoperative mitomycin
Whitson, 2009[128] Cohort 42 Low	Multivariate HR: 6.7 (2.1 to 22.1) p<0.01	Age, smoking, radiotherapy, diabetes mellitus, hypertension, hyperlipidemia, CRI, immunosuppression, recurrence rate, whether the tumor was primary or recurrent, multiple tumors, tumor >3 cm, stage T1, high grade, CIS, EORTC score >6, positive cytology, and positive UroVysion

Abbreviations: CI = confidence interval; CIS = carcinoma in situ; cm = centimeter; CRI = chronic renal insufficiency; EORTC = European Organization for Research and Treatment of Cancer; HR = hazard ratio; N = number; p = probability.

UroVysion Cancer-Specific Survival

We found no studies meeting our inclusion criteria.

UroVysion Overall Survival

We found no studies meeting our inclusion criteria.

Key Question 4a: Influence on Physician Decision

We identified studies evaluating the influence of molecular pathology tests for RR on treatment decisionmaking for three of the tests of interest, the Oncotype DX and MammaPrint assays for breast cancer, and Oncotype DX Colon. For Oncotype DX Colon, none of the included studies were rated as low or medium RoB. For Oncotype DX Breast and MammaPrint, the studies available for review included a mix of prospective and retrospective cohort studies and uncontrolled trial designs, with a larger body of literature examining the use of Oncotype DX than MammaPrint. No studies examined the effect of the two assays compared with each other.

Characteristics of Included Studies Assessing Oncotype DX Breast and Treatment Decisions

For Oncotype DX Breast, we included six cohort studies (total N=990 patients) and ten uncontrolled trials (total N=1,261 patients) rated as low or medium RoB (Table 37). One additional uncontrolled trial[130,131] was excluded from our main analysis because of an unclear RoB rating and is not included in this summary. Most of the studies were performed at single academic centers or in multicenter studies in the United States, but studies performed at centers in Europe, Canada, Australia, Mexico, Japan and Israel were also found. The studies uniformly examined cohorts with hormone-receptor positive breast cancer, and most were limited to women with node-negative cancers. The mean age of patients in the studies varied from 48 to 61 years.

Table 37. Characteristics of included studies: Oncotype DX Breast and treatment decisions

Author, Year Test (Cancer Type) Risk of Bias	N Study Type	Country(ies)	Disease Stage(s) Other Tumor/Disease Characteristics	Overall Age (years) % Female
Ademuyiwa, 2011[132] Oncotype DX (breast) Medium	276 patients 2 oncologists Pre-post-test design and uncontrolled trial	United States	Node negative, ER+, HER2/neu−	Median: 55; Mean (range): 54.8 (29 to 82) 100%
Albanell, 2011[133] Oncotype DX (breast) Low	107 Uncontrolled trial	Spain	Node negative, ER+, HER2−	NR 100%
Bargallo, 2012[134] Oncotype DX (breast) Medium	96[a] Uncontrolled trial	Mexico	ER+, HER2-, stage I-IIIa, node-negative or –positive (1-3 nodes)	NR 100%
Davidson, 2013[135] Oncotype DX (breast) Medium	150 Uncontrolled trial	Canada	I–II ER+, HER2−, node negative	Mean (range): 53 (23 to 78) 100%

Table 37. Characteristics of included studies: Oncotype DX Breast and treatment decisions (continued)

Author, Year Test (Cancer Type) Risk of Bias	N Study Type	Country(ies)	Disease Stage(s) Other Tumor/Disease Characteristics	Overall Age (years) % Female
de Boer, 2013[136] Oncotype DX (breast) Medium	151 Uncontrolled trial	Australia	Early stage, T1 – T3 Unifocal ER+/-, PR+/-, HER2− , node negative or node positive (1–3 positive nodes, including micrometastases and isolated tumor cells)	Mean: 56.2 100%
Eiermann, 2013[137] Oncotype DX (breast) Low	366 Cohort	Germany	Early breast cancer ER+, HER2−, node negative or histologically verified lymph node metastases in up to three lymph nodes	Mean: 56 100%
Geffen, 2011[138] Oncotype DX (breast) Medium	135 Cohort	Israel	I–II ER+ or ER−, PR+ or PR−, HER2+ or HER−	Median 58 (33–75) years 97.8%
Gligorov, 2012[130] Oncotype DX (breast) Unclear	92 patients NR oncologists Uncontrolled trial	France	ER+, HER2−, node negative or pN1 (mi) breast cancer	NR NR
Henry, 2009[139] Oncotype DX (breast) Low	29 Cohort	United States	I–II Node negative, ER+	Median (range): 51 (31 to 74) 96.5%
Holt, 2013[140] Oncotype DX (breast) Medium	142 Uncontrolled trial	United Kingdom	T1 – T3 ER+, node negative invasive breast cancer or minimal node involvement	Median (range): 55 (34 – 72) 100%
Joh, 2011[141] Oncotype DX (breast) Low	95 patients' records Survey participants: 4 surgical oncologists; 4 medical oncologists; 4 pathologists Pre-post-test design; Uncontrolled trial	United States	Early stage, ER-positive breast cancer	Median overall age of patients is NR Patients with RS<18: Median: 54 years; Mean (SD) 55.5 (1.1) Patients with RS 18–30: Median 51 years, Mean (SD) 53.4 (1.3) Patients with RS >30: Median 58.5, Mean (SD) 59.1 (3.3) 100%
Kamal, 2011[142] Oncotype DX (breast) Medium	31 Uncontrolled trial	United States	Early stage ER+, node negative	Median (range): 53 (42–82) NR
Klang, 2010[143] Oncotype DX (breast) Low	313 Cohort	Israel	NR	Mean (range): 57 (29–81) 99%
Lo, 2010[144] Oncotype DX (breast) Low	17 oncologists 89 patients Uncontrolled trial	United States	I-II ER+, node negative	Mean (range): 55 (35–77) 100%

Table 37. Characteristics of included studies: Oncotype DX Breast and treatment decisions (continued)

Author, Year Test (Cancer Type) Risk of Bias	N Study Type	Country(ies)	Disease Stage(s) Other Tumor/Disease Characteristics	Overall Age (years) % Female
Rayhanabad, 2012[145] Oncotype DX (breast) Low	58 Cohort	United States	T1–T2 Node-negative, ER+	Mean (range): 54 (26–78)
Schneider, 2012[146] Oncotype DX (breast) Medium	89 Cohort	United States	ER+, node negative	NR 100%
Yamauchi, 2013[147] Oncotype DX (breast) Medium	124 patients 17 physicians Uncontrolled trial	Japan	Invasive early breast cancer ER+, HER2- 0 to 3 positive lymph nodes	Mean: 51.4 100%

[a]100 were enrolled; 96 were analyzed; 2 did not have assay results and outcome data were missing for 2.

Abbreviations: ER = estrogen receptor; HER = Human Epidermal Growth Factor; HER2 = Human Epidermal Growth Factor Receptor 2, also known as Neu; HR = hazard ratio; N = number; NR = not reported; PR = progesterone receptor; RS = risk score; SD: standard deviation.

Results: Oncotype DX and Treatment Decisions

Across studies, the percentage of patients whose recommendation for treatment was changed by the Oncotype test result was generally around 30 percent, ranging from 14 percent to 40 percent. Although treatment decision changes were observed in both directions for individual patients, all studies consistently showed a pattern of a shift to less-intensive treatment recommendations (more patients moving from chemotherapy plus hormonal therapy to hormonal therapy alone than from hormonal therapy to combination therapy) as a result of including the Oncotype score in decisionmaking information (Table 38).

One cohort study[139] also included a nested uncontrolled trial in which a panel of five experts provided treatment recommendations with and without the Oncotype score for patients included in the observational cohort; results were consistent with the other studies.

Table 38. Impact of test results on treatment decisions

Author, Year, Design, N, Test (Cancer), Risk of Bias	Decisions Based on Molecular Pathology Test Results Combined With Standard Prognostic Markers	Decisions Based on Standard Prognostic Markers Alone
Ademuyiwa, 2011[132] Pre-post-test design an uncontrolled trial 276 Oncotype DX (breast) Medium	ODX score OR: 1.23, 95% CI 1.16 to 1.29, p<0.001 Overall change: 38%	71/188 no CTX patients: recommended for CTX based on ODX blinded records review. 34/88 CTX patients; recommended for no CTX based on ODX blinded records review.

Table 38. Impact of test results on treatment decisions (continued)

Author, Year, Design, N, Test (Cancer), Risk of Bias	Decisions Based on Molecular Pathology Test Results Combined With Standard Prognostic Markers	Decisions Based on Standard Prognostic Markers Alone
Albanell, 2011[133] Uncontrolled trial 107 Oncotype DX (breast) Low	Overall change: 34 (32%; 95% CI 26% to 34%) CTX to no CTX: 22 (21%; 95% CI 19.6% to 21.6%) No CTX to CTX: 12 (11%; 95% CI 10.6% to 11.8%) In each group: No CTX to CTX: 12 of 68 (18%) CTX to no CTX: 22 of 39 (56%) CTX in each RS group: Total CTX: 29 of 107 (27%) Low RS: 2/62 (3%) Intermediate RS: 17/35 (49%) High RS: 10/10 (100%)	CTX: 39 (36%) No CTX: 68 (64%) CTX in each RS group: Low RS: 22 (35%) Intermediate RS: 9 (26%) High RS: 8 (80%)
Bargallo, 2012[134] Uncontrolled trial 96 Oncotype DX (breast) Medium	Overall change: 14% Proportion recommended CTX decreased from 48% to 34% (p=0.024). Decrease by subgroups: 6% decrease in N0 patients, and 26% in N_{mic} and N1-3 patients. Net decrease in chemotherapy recommendations: 13/96 = 14% (95% CI 7%-22%).	HT: 50 (52%) CHT: 46 (48%)
Davidson, 2013[135] Uncontrolled trial 150 Oncotype DX (breast) Medium	Overall change: 45 (30%) (95% CI: 22.8 to 38.0%) CTX to no CTX: 20% (95% CI 13.9 to 27.3%) No CTX to CTX: 10% (95% CI 5.7 to 16.0%) CTX in each RS group: Total CTX: 47 (31.3%) [percentage change overall=−10] Low RS: 0 [percentage change=−29] Intermediate RS: 13 [percentage change=−11] High RS: 34 [percentage change=+28]	CTX: 62 (41.3%) CTX in each RS group: Low RS: 20 Intermediate RS: 18 High RS: 24
De Boer, 2013[136] Uncontrolled trial 151 Oncotype DX (breast) Medium	Node negative: Overall change: 24% HTX to CTX+HTX: 12/71 (17%) CTX+HTX to HTX: 12/30 (40%) Node positive: Overall change: 26% HTX to CTX+HTX: 1/13 (8%) CTX+HTX to HTX: 12/37 (32%)	Node negative: Treatment plan pre-RS HTX=71 (70%) CTX+HTX=30 (30%) Node positive: Treatment plan pre-RS HTX=13 (26%) CTX+HTX=37 (74%)

Table 38. Impact of test results on treatment decisions (continued)

Author, Year, Design, N, Test (Cancer), Risk of Bias	Decisions Based on Molecular Pathology Test Results Combined With Standard Prognostic Markers	Decisions Based on Standard Prognostic Markers Alone
Eiermann, 2013[137] Cohort 366 Oncotype DX (breast) Low	Overall change: 33% 95 CI (28.3, 38.1); CTX=HTX to HTX: 22% HTX to CTX+HTX: 11% Other: 1% Node negative overall change: 30% change 95% CI (24.6, 36.5) CTX+HTX to HTX: 18% HTX to CTX+HTX: 12% CTX+HTX to CTX: 1 patient Node positive: Overall change: 39% 95% CI (29.9, 47.8); CTX+HTX to HTX: 28% HTX to CTX+HTX: 9% Observation to HTX or CTX+HTX: 2%	CTX+HTX overall: 209 (57%) CTX+HTX node negative: 48% CTX+HTX node positive: 75%
Geffen, 2011[138] Cohort 135 Oncotype DX (breast) Medium	Overall change: 34 (25.2%; 95% CI 17.9% to 32.5%) CTX to HTX: 24 (17.8%; 95% CI 11.3% to 24.2%) HTX to CTX: 10 (7.4%; 95% CI 2.9% to 11.8%) CTX in each risk group Low risk: 10% Intermediate risk: 55% High risk: 35% No CTX in each risk group Low risk: 72% Intermediate risk: 28% High risk: 0%	CTX: 63 (47%) No CTX: 72 (53%) CTX in each risk group: Low risk: 41% Intermediate risk: 41% High risk: 17% No CTX in each risk group Low risk: 57% Intermediate risk: 35% High risk: 8%
Henry, 2009[139] Cohort 29 Oncotype DX (breast) Low	Treating physicians: Overall change: 9 (31%) CTX to no CTX: 7 of 13 patients (54%) No CTX to CTX: 2 of 16 (13%) Expert panel: Overall change: 7 (24%) CTX to no CTX: 5 of 12 patients (42%) No CTX to CTX: 2 of 17 (12%)	Treating physicians: CTX: 13 (45%) HTX: 16 (55%) Expert panel: CTX: 12 (41%) HTX: 17 (59%)
Holt, 2013[140] Uncontrolled trial 142 Oncotype DX (breast) Medium	Overall change: 38 (26.76%) CTX + HT to HT: 26/57 (45.61%) HT to CTX+HT: 12/85 (14.12%)	Overall: CTX + HT: 57 (40.14%) HT: 85 (59.86%)

Table 38. Impact of test results on treatment decisions (continued)

Author, Year, Design, N, Test (Cancer), Risk of Bias	Decisions Based on Molecular Pathology TestResults Combined With Standard Prognostic Markers	Decisions Based on Standard Prognostic Markers Alone
Joh, 2011[141] Pre-post-test design and uncontrolled trial 95 patients' records Survey participants: 4 surgical oncologists, 4 medical oncologists, 4 pathologists Oncotype DX (breast) Low	Overall change: 24.9% % overtreated: 69.0% +/− 6.9% (range 5.9 to 85.7) p=0.0322 (compared with treatment decisions made with standard prognostic markers alone)	% Over treated: 82.3% +/− 1.3% (range 75.5 to 89.0)
Kamal, 2011[142] Uncontrolled trial 31 Oncotype DX (breast) Medium	Overall change: 19% of 31 cases changed 5 oncologists recommended chemotherapy in 10%–19% of 31 cases; 1 oncologist recommended chemotherapy in 58% of 31 cases Type of changes in chemotherapy recommendation (N=186 scenarios): No change, 151 (81.2%) CTX to no CTX: 20 (10.8%) No CTX to CTX: 15 (8.1%) Odds ratio of actual Oncotype DX RS changing chemotherapy recommendation: High vs. low: OR=82.650 (95% CI, 8.959 to 762.496) Intermediate vs. low: OR=6.463 (95% CI, 1.682 to 24.841)	5 oncologists recommended chemotherapy in 16% to 23% of the 31 cases; 1 oncologist recommended chemotherapy in 52% of 31 cases
Klang, 2010[143] Cohort 313 Oncotype DX (breast) Low	Overall change: 125 (40%) CTX to no CTX: 105 (34%)	CTX: 174 (56%)

Table 38. Impact of test results on treatment decisions (continued)

Author, Year, Design, N, Test (Cancer), Risk of Bias	Decisions Based on Molecular Pathology TestResults Combined With Standard Prognostic Markers	Decisions Based on Standard Prognostic Markers Alone
Lo, 2010[144] Uncontrolled trial 17 oncologists; 89 patients Oncotype DX (breast) Low	Overall change: 28 (31.5%) No CTX to no CTX: 40 (44.9%) No CTX to CTX: 3 (3.4%) CTX to no CTX: 20 (22.5%) CTX to CTX: 20 (22.5%) No CTX to equipoise: 3 (3.4%) CTX to equipoise: 2 (2.2%) Equipoise to equipoise: 1 (1.1%) HER2/neu-positive subset (N=6) CTX to no CTX: 1 (16.6%) CTX to CTX: 4 (66.7%) No CTX to no CTX: 1 (16.6%) (Note: equipoise is defined as equal options of either CTX, no CTX, or enrollment onto the TAILORx clinical trial, where patients would be randomly assigned between CTX followed by no CTX or no CTX alone)	CTX: 42 (47%), No CTX: 46 (51.7%) Either CTX or no CTX to one patient (1.1%)
Rayhanabad, 2012[145] Cohort 58 Oncotype DX (breast) Low	Overall change: 15/58 patients (26%) 23 (40%) low risk by RS 30 (51%) intermediate risk by RS 5 (9%) high risk by RS ODX increased the number of patients classified as low risk by 12% No CTX to CTX: 2/16 CTX to No CTX: 13/42	No CTX: 16 (28%) low risk by National Comprehensive Cancer Network CTX: 42 (72%) high risk by National Comprehensive Cancer Network
Schneider, 2012[146] Cohort 89 Oncotype DX (breast) Medium	Overall change: 45% CTX to HT: 39% HT to CTX: 4.5%	CTX: 61% HT: 39%

Table 38. Impact of test results on treatment decisions (continued)

Author, Year, Design, N, Test (Cancer), Risk of Bias	Decisions Based on Molecular Pathology Test Results Combined With Standard Prognostic Markers	Decisions Based on Standard Prognostic Markers Alone
Yamauchi, 2013[147] Uncontrolled trial 124 patients 17 physicians Oncotype DX (breast) Medium	Change in treatment recommendations among all patients: 47/124 patients (38%) Change in treatment recommendations for N0 patients: 34/104 patients (33%) Change in treatment recommendations for N+ patients: 13/20 patients (65%) CHT to HT: 40/63 patients (63%) CHT to HT in N0 patients: 27/48 patients (56%) CHT to HT in N+ patients: 13/15 patients (87%) HT to CHT: 7/61 patients (11%) HT to CHT in N0 patients: 7/56 patients (13%) HT to CHT in N+ patients: 0 patients (0%)	CHT: 63/124 patients (51%) HT: 61/124 patients (49%)

Abbreviations: CI = confidence interval; CHT = chemohormonal therapy; CTX = chemotherapy; HER2/neu = Human Epidermal Growth Factor Receptor 2, also known as Neu; HT = hormonal therapy; HTX = hormone treatment; N = number; NR = not reported; ODX = original diagnosis; RS= risk score; TAILORx = Tailored treatment; vs. = versus.

Characteristics of Included Studies Assessing MammaPrint and Treatment Decisions

We included one cohort study regarding decisionmaking (Table 39). This study was performed entirely in the Netherlands and included 427 women with a median age of 48 years and with node-negative invasive breast cancers. None of the patients were over 65 years of age. In the cohort study, physicians' treatment recommendations based on Dutch clinical guidelines were compared with recommendations based on the combination of clinical guidelines and the MammaPrint result.[148]

Table 39. Characteristics of included studies: MammaPrint and treatment decisions

Author, Year Test (Cancer Type) Risk of Bias	N Study Type	Country(ies)	Disease Stage(s) Other Tumor/Disease Characteristics	Overall Age (years) % Female
Bueno-de-Mesquita, 2007[148] MammaPrint (breast) Low	427 Pre-post-test design an uncontrolled trial	The Netherlands	T I–IIII Node negative	Mean (SD): 48 (7); Median (range) 49 (27 to 60) 100%

Abbreviations: N = number; SD: standard deviation.

Results: MammaPrint and Treatment Decisions

The addition of the MammaPrint test result increased the percentage of patients recommended to receive some form of adjuvant therapy (either hormonal therapy, chemotherapy, or both) from 48 to 62 percent. However, the greatest increase was among women moving from no therapy to hormonal therapy. One significant limitation of this study for application to the U.S. population is that Dutch treatment guidelines during the study period were unusually restrictive in terms of indications for breast cancer adjuvant therapy compared with more widely accepted guidelines in the United States; specifically, women with hormone-receptor positive breast cancers would be uniformly recommended to receive hormonal therapy under U.S. guidelines.

Characteristics of Included Studies Assessing Oncotype DX Colon and Treatment Decisions

We identified three eligible studies (Table 40). Two were conducted in the United States and one in Israel. One cross-sectional survey assessed the treatment decisions of 116 physicians;[149] one uncontrolled trial assessed treatment decisions of 105 oncologists;[150] and one cohort study examined treatment recommendations before assay results compared with actual treatment received after assay results for 269 patients.[151] One study was rated as high RoB and two were rated as unclear RoB. Appendix C provides additional rationale for RoB ratings.

Table 40. Characteristics of included studies: Oncotype DX Colon and treatment decisions

Author, Year Test (Cancer Type) Risk of Bias	N Study Type	Country(ies)	Disease Stage(s) Other Tumor/Disease Characteristics	Overall Age (years) % Female
Brenner, 2013[151] Oncotype DX (colorectal) High	269 patients Cohort	Israel	II	NR (but reported 48% were at least 70 years old) NR
Cartwright, 2012[149] Oncotype DX (colorectal) High	116 physicians 92 patients Cross-sectional survey	United States	II	Mean (SD): 61.3 (11.8) NR
Srivastava, 2013[150] Oncotype DX (colorectal) Unclear	105 oncologists 141 patients Uncontrolled trial	United States	II	NR NR

Abbreviations: N = number; NR = not reported; SD = standard deviation.

Results: Oncotype DX Colon and Treatment Decisions

With no studies rated as low or medium RoB, we found no reliable data to inform conclusions about the impact of the Oncotype DX Colon test on treatment decisions.

Key Question 4b: Clinical Utility—Evidence that Modified Decisions Lead to Improved Outcomes

We found no eligible studies that addressed this question.

Key Question 5. Harms Associated with Treatment Decisions that are Informed by Molecular Pathology Tests

We found no eligible studies that addressed this question.

Discussion

Below, we summarize the main findings and strength of evidence (SOE). We then discuss implications for decision-making, limitations, future research, and conclusions.

Key Findings and Strength of Evidence

We found no studies that directly addressed our overarching question (Key Question [KQ] 1) (i.e., no studies directly assessed the impact of a test of interest on physician decision-making and subsequent health outcomes). Further, no studies directly addressed whether modified decisions lead to improved health outcomes (KQ 4b, clinical utility), and none reported harms associated with treatment decisions that are informed by molecular pathology tests (KQ 5).

The majority of studies meeting inclusion criteria for our review focused on clinical validity (KQ 3), and they evaluated associations between prognostic tests and outcomes. For two tests, MammaPrint and Oncotype DX Breast, we found studies rated as low or medium risk of bias (RoB) addressing whether prognostic information provided by the molecular pathology tests modified treatment decisions (KQ 4a).

Analytic Validity

Of the six molecular pathology tests with studies of low or medium RoB, the *EGFR* and *KRAS* mutation tests for lung cancer, the MammaPrint test for breast cancer, and the *KRAS* mutation test for colorectal cancer (CRC) were determined to have an overall moderate or high SOE for analytic validity (Table 41). Studies of these tests used fairly large panels of samples, were all low RoB, were directly measuring the test, and were consistent in their measurements.

Table 41. Summary of findings and strength of evidence for analytic validity

Test	Parameter	N studies; N subjects	Value	Strength of Evidence
MammaPrint: Breast	SS	2;399	NR	Moderate
	CV	1;100	NA	Low
EGFR: Lung:	SS	5; 898	Sensitivity range: 68–100%; Specificity range: 79–100%	Moderate
	CV	5;636	Kappa score range: 0.20–0.73	High
KRAS: Lung:	SS	2;188	NR	Moderate
	CV	4;686	Kappa score range: 0.15–0.66	High
BRAF: Colorectal	SS	1;117	NR	Insufficient
	CV	3;533	NA	High
KRAS: Colorectal	SS	5;576	Sensitivity range: 69–98%; Specificity range: 90–100%	High
	CV	5;747	Reproducibility: 98%	High
Oncotype DX: Colorectal:	SS	1; NR	NR	Insufficient [
	CV	NA	NA	NA

Abbreviations: *BRAF* = gene name; CV = cross-lab validity; *EGFR* = gene name; *KRAS* = gene name; N = number; NA = not applicable; NR = not reported; SS = sensitivity and specificity.

The SOE for the overall analytic validities of the *BRAF* mutation test for CRC and the Oncotype DX Colon multigene assay for CRC were determined to be low. There were only one or two studies to consider, RoB was generally higher, and consistency was often

unknown (when there was a single study). However, the *BRAF* mutation test for CRC, due to the CAP report data, showed a high SOE for cross-lab validity.

In general, we found limited evidence in the published literature assessing analytic validity of the included tests. For most of these tests, we found evidence from fewer than 200 subjects; just 2 of the tests (*EGFR*/Lung and *KRAS*/CRC) had more than 200 samples contributing to our SOE grade (Table 41).

However, the best data on reproducibility we found is from the College of American Pathologists' report data for *EGFR* mutation testing, *KRAS* mutation testing, *BRAF* mutation testing, microsatellite instability for colorectal cancer, and UroVysion cytogenetics for urinary bladder cancer, which support the analytic validity of these tests.

In general, in most of the studies, tests were developed in the laboratories and compared with the gold standard of direct Sanger sequencing of the gene in formalin-fixed, paraffin-embedded tissue samples. We had very few studies directly assessing the analytic validity (test performance) using direct sequencing of frozen tissue (the current gold standard), which would be of great importance in determining the true analytic validity of the tests.

In general, the studies showed that their tests in comparison with the gold standard were of comparable marker sensitivity/specificity and had similar proportions of valid results (level of detection). Because the analytic validity, sensitivity, and specificity of direct sequencing of frozen tissue have not been established against their "true" tumor diagnosis, the false-positive rate cannot truly be determined for the other tests used in these studies. In Beau-Faller et al.,[35] the false positive rate for direct sequencing of *EGFR* and *KRAS* was stated to be about 10 to 15 percent. Therefore, any numbers we have given for marker sensitivity/specificity and predictive value are estimates, assuming accurate direct sequencing.

Clinical Validity

Included studies provided some evidence on clinical validity for 9 of the included tests, adjusted for known prognostic factors (Table 42). Evidence from multiple studies supports prognostic value , beyond known prognostic factors, for MammaPrint, Oncotype DX Breast, *KRAS* mutation testing for lung cancer, *BRAF* mutation testing for CRC, *KRAS* mutation testing for CRC, and microsatellite instability (MSI) for CRC for at least one of our included outcomes (i.e., risk of recurrence [RR], cancer-specific survival [CSS], or overall survival [OS]). For UroVysion, limited evidence from 2 small studies (total N=168) rated as low or medium RoB supported prognostic value for RR. None of the studies we evaluated suggested that *EGFR* added prognostic value to the traditional factors used to determine prognosis for lung cancer. For CRC, evidence did not adequately support added prognostic value for Oncotype DX Colon.

Table 42. Summary of findings on clinical validity (i.e., Association between Test Result and Prognosis)

Test: Cancer	Outcome	N studies; N subjects	Results Effect Size (95% CI)	Evidence from Multiple Studies Supports Association between Test Result and Prognosis?
MammaPrint: Breast	RR	6; 1,913	HR: 2.84 (2.11 to 3.89) for poor prognosis vs. good prognosis	Yes
	CSS	5; 1,615	HR: 3.3 (2.22 to 4.9) for poor prognosis vs. good prognosis	Yes
	OS	1; 144	HR: 1.67 (0.73 to 3.82) for poor prognosis vs. good prognosis	No
Oncotype DX Breast	RR	6; 3,222	HR: 2.97 (2.19 to 4.02) for high risk vs. low risk	Yes
	CSS	2; 1,234	HR: 2.02 (1.35 to 3.00) for high risk vs. low risk	Yes
	OS	1; 668	HR: 1.65 (1.24 to 2.19) for high risk vs. low risk	No, single study
EGFR: Lung	RR	6; 1,870	HR: 0.87 (0.65 to 1.15); No association	No
	CSS	0; 0	NA	No
	OS	6; 1,820	HR: 0.76 (0.50 to 1.19); No association	No
KRAS: Lung	RR	4; 611	2.84 (1.14, 7.1) *KRAS* mutation associated with greater RR	Yes
	CSS	0; 0	NA	No
	OS	2; 253	2.69 (1.91,3.8); 3.33 (1.03, 10.82)	Yes[a]
BRAF: CRC	RR	5; 4,106	HR 1.07 (0.76 to 1.52) for wild-type vs. mutation	No
	CSS	7; 5,409	HR 1.50 (1.26 to 1.77) for wild-type vs. mutation	Yes
	OS	11;7,610	HR 1.45 (1.29 to 1.62) for wild-type vs. mutation	Yes
KRAS: CRC	RR	5; 4,085	HR 1.02 (0.91 to 1.14) for wild-type vs. mutation	No
	CSS	2; 1,174	HR 1.30 (1.02 to 1.66) for wild-type vs. mutation	Yes
	OS	10; 5,328	HR 1.22 (0.93 to 1.60) for wild-type vs. mutation	No
MSI: CRC	RR	10; 7,130	HR 0.60 (0.50 to 0.72) for MSI-H vs. MSS	Yes
	CSS	6; 3,439	HR 0.65 (0.51 to 0.82) for MSI-H vs. MSS	Yes
	OS	12; 8,839	HR 0.57 (0.43 to 0.77) for MSI-H vs. MSS	Yes
Oncotype DX: CRC	RR	1; 690	HR 1.68 (1.18 to 2.38)	No, single study
	CSS	0; 0	NA	No
	OS	0; 0	NA	No
UroVysion: Bladder	RR	2; 168	Association between mutation and RR in 2 small studies	Yes, but limited to 168 subjects
	CSS	0; 0	NA	No
	OS	0; 0	NA	No

[a] Data synthesiswas done only when we had 3 or more HRs to combine to create a summary.

Notes: Table includes results of our main analyses that were based on studies rated as low or medium RoB. HRs reported are results of our meta-analyses of studies rated as low or medium RoB reporting adjusted associations for clinical validity (KQ 3).

Abbreviations: *BRAF* = gene name; CRC = colorectal cancer; CSS = cancer-specific survival; *EGFR* = gene name; HR = hazard ratio; *KRAS* = gene name; MSI = microsatellite instability; MSI-H = microsatellite instability high; MSS = microsatellite stability: N = number; NA = not applicable; OS = overall survival; RR = risk of recurrence; vs. = versus.

Breast Cancer: MammaPrint

Our meta-analysis suggests that patients classified as having a poor prognosis by MammaPrint consistently do worse than those with a good prognosis signature with respect to distant metastatis-free survival and CSS. Studies included in the search varied somewhat in the subpopulations they tested; the fact that the signature added prognostic

value across these various subpopulations suggests that it has broad applicability. Because no studies looked at the value of MammaPrint with respect to loco-regional recurrence (LRR) and only one considered overall survival, there is scant or no evidence regarding the clinical validity of the MammaPrint signature in terms of these outcomes.

Breast Cancer: Oncotype DX

Some evidence indicates that the risk score (RS) estimated by Oncotype DX adds prognostic value in predicting distant recurrence and CSS. The two included studies that used LRR as an outcome reported that the RS does not add value in determining prognosis (with respect to LRR). Thus, evidence suggests that the Oncotype DX score adds value in determining prognosis for distant metastasis and CSS but not for LRR.

Lung Cancer: KRAS mutation

Some evidence suggest that testing for KRAS mutations has added prognostic value in lung cancer for both RR and OS. Our meta-analysis resulted in significant HRs for both RR and OS. There were no studies that looked at CSS. The results seem to hold for all stages. However, because the studies did not examine differences by race, age, or gender, it is not known if the prognostic value of the mutation varies by any of these factors.

Colorectal Cancer: *BRAF* Mutation

Evidence suggests that *BRAF* mutation does not have added prognostic value for RR. But our meta-analysis found that *BRAF* mutation testing has prognostic value for CSS and OS. The populations studied included proximal and distal colon cancers as well as rectal cancers. The studies did not examine if the risk varied by race, age, or gender. The results seem to hold for proximal, distal, and rectal cancers. However, because the studies did not examine differences by race, age, or gender, it is not known if the prognostic value of the mutation varies by any of these factors.

Colorectal Cancer: *KRAS* Mutation

Evidence suggests that *KRAS* mutation does not have added prognostic value for RR or OS. But our meta-analysis found that *KRAS* mutation testing has prognostic value for CSS. The populations studied included proximal and distal colon cancers as well as rectal cancers. The studies did not examine if the risk varied by race, age, or gender. The results seem to hold for proximal, distal, and rectal cancers. However, because the studies did not examine differences by race, age, or gender, it is not known if the prognostic value of the mutation varies by any of these factors.

Colorectal Cancer: MSI

Our meta-analyses found that testing for MSI adds prognostic value with respect to RR, CSS, and OS in CRC patients. Patients with MSI-H tumors have a lower risk of recurrence, death due to CRC, and death due to any cause compared with patients with MSS tumors.

The studies included looked at proximal, distal, and rectal cancers but did not look for differences by race, age, or gender. Thus, although it is possible to say that in general

MSI-H has a protective effect for CRC patients, evidence was lacking to allow determination of whether protection varies by race, age, or gender.

Clinical Utility and the Overarching Question

We found no studies that directly addressed our overarching question (KQ 1) (i.e., no studies directly assessed the impact of test use on downstream health outcomes). We attempted to construct an indirect chain of evidence to answer the overarching question, but no studies addressed whether modified decisions lead to improved health outcomes (KQ 4b, clinical utility), so we were unable to do so. The furthest downstream evidence that we found addressed whether prognostic information provided by the molecular pathology tests modifies treatment decisions (KQ 4a); we found such evidence for three tests, MammaPrint, Oncotype DX Breast, and Oncotype DX Colon (but the three studies identified for Oncotype DX Colon were rated as high or unclear risk of bias).

For impact on treatment decisions, we found moderate SOE that one test, Oncotype DX Breast, leads to changes in decisions. Although the decision changes were observed in both directions for individual patients, studies consistently showed an overall shift to less-intensive treatment recommendations as a result of using Oncotype DX Breast, with fewer recommendations for chemotherapy (and therefore less exposure to potential harms of chemotherapy; but studies did not follow patients to actually report on harms or to assess the overall balance of clinical benefits and harms).We found just one study of low or medium RoB for the impact of MammaPrint on treatment decisions, and we concluded that evidence was insufficient to determine the impact of MammaPrint on treatment decisions, primarily because of unknown consistency and imprecision.

Table 43 summarizes the evidence on the overarching question, clinical utility, and the impact of test use on treatment decisions. Ultimately, for the reasons described above, we found insufficient SOE to answer the overarching question for most tests. Even in the cases where the tests seemed to add value in determining prognosis (i.e., evidence of clinical validity), we found no direct evidence that using the test was related to improved outcomes for patients. For a few tests, we found low SOE, suggesting that using the test would not improve outcomes for patients—for these tests we found evidence that did not support clinical validity (because with evidence suggesting lack of clinical validity, it is unlikely that the tests will be found to have clinical utility).

Table 43. Summary of findings and strength of evidence for impact on treatment decisions, clinical utility, and our overarching question

Test: Cancer	Outcome	N studies; N subjects	Conclusions	Strength of Evidence
MammaPrint: Breast	RR	6; 1,913	All studies assessed clinical validity; no evidence that test use leads to improved outcomes	Insufficient
	CSS	5; 1,615	All studies assessed clinical validity; no evidence that test use leads to improved CSS	Insufficient
	OS	1; 144	Study assessed clinical validity; no evidence that test use leads to improved morality	Insufficient
	Decisions about Rx	1; 427	Adjuvant therapy was used less if the prognosis signature is used	Insufficient
Oncotype DX Breast	RR	6; 3,222	All studies assessed clinical validity; no evidence that test use leads to improved outcomes	Insufficient
	CSS	2; 1,234	All studies assessed clinical validity; no evidence that test use leads to improved CSS	Insufficient
	OS	1; 668	All studies assessed clinical validity; no evidence that test use leads to improved mortality	Insufficient
	Decisions about Rx	16; 2,251	~30% of treatment decisions changed by the test	Moderate
EGFR: Lung	RR	6; 1,870	All studies assessed clinical validity and found no prognostic value; test is unlikely to improve outcomes	Low
	CSS	0; 0	NA	Insufficient
	OS	6;1,820	No prognostic value; none of the reported HRs were statistically significant; test unlikely to improve mortality	Low
	Decisions about Rx	0; 0	NA	Insufficient
KRAS: Lung	RR	4; 611	All studies assessed clinical validity; no evidence that test use leads to improved outcomes	Insufficient
	CSS	0; 0	NA	Insufficient
	OS	2; 253	Studies assessed clinical validity; no prognostic value; no evidence that test use leads to improved mortality	Insufficient
	Decisions about Rx	0; 0	NA	Insufficient
BRAF: CRC	RR	5; 4,106	All studies assessed clinical validity; no prognostic value; test is unlikely to improve outcomes	Low
	CSS	7; 5,409	All studies assessed clinical validity; no evidence that test use leads to improved CSS	Insufficient
	OS	10; 7,610	All studies assessed clinical validity; no evidence that test use leads to improved mortality	Insufficient
	Decisions about Rx	0; 0	NA	Insufficient
KRAS: CRC	RR	5; 4,085	All studies assessed clinical validity; no prognostic value; test is unlikely to improve outcomes	Low
	CSS	2; 1,174	All studies assessed clinical validity; no evidence that test use leads to improved outcomes	Insufficient
	OS	10; 5,328	All studies assessed clinical validity; no prognostic value; test is unlikely to improve mortality	Low
	Decisions about Rx	0; 0	NA	Insufficient
MSI: CRC	RR	10; 7,130	All studies assessed clinical validity; no evidence that test use leads to improved outcomes	Insufficient
	CSS	6; 3,439	All studies assessed clinical validity; no evidence that test use leads to improved CSS	Insufficient
	OS	12; 8,839	All studies assessed clinical validity; no evidence that test use leads to improved mortality	Insufficient
	Decisions about Rx	0; 0	NA	Insufficient

Table 43. Summary of findings and strength of evidence for impact on treatment decisions, clinical utility, and our overarching question (continued)

Test: Cancer	Outcome	N studies; N subjects	Conclusions	Strength of Evidence
Oncotype DX: CRC	RR	1; 690	Study assessed clinical validity; no evidence that test use leads to improved outcomes	Insufficient
	CSS	0; 0	NA	Insufficient
	OS	0; 0	NA	Insufficient
	Decisions about Rx	0; 0	NA	Insufficient
UroVysion: Bladder	RR	2; 168	Both studies assessed clinical validity; no evidence that test use leads to improved outcomes	Insufficient
	CSS	0; 0	NA	Insufficient
	OS	0; 0	NA	Insufficient
	Decisions about Rx	0; 0	NA	Insufficient

Notes: Table included results of our main analyses that were based on studies rated as low or medium RoB. HRs reported are results of our meta-analyses of studies rated as low or medium RoB reporting adjusted associations for clinical validity (KQ 3).

Strength of evidence grades are for the overarching question not for clinical validity (i.e., not for prognostic value or accuracy).

Abbreviations: *BRAF* = gene name; CRC = colorectal cancer; CSS = cancer-specific survival; *EGFR* = gene name; HR = hazard ratio; *KRAS* = gene name; MSI = microsatellite instability; N = number; NA = not applicable; OS = overall survival; RR = risk of recurrence; Rx = treatment.

Implications for Clinical and Policy Decisionmaking

Our review demonstrated that the weight of published research to date in the area of molecular pathology tests for improving estimates of cancer prognosis has focused on the clinical validity of the tests of interest in giving information about prognosis and little emphasis on how these tests can be integrated into the overall care of cancer patients in terms of measuring changes in management decisions or the effect of those altered decisions on downstream outcomes of value to patients. Such changes in management may be occurring and may be of benefit, or possibly of harm, to patients but have not been measured and studied, with the notable exception of the Oncotype DX assay in breast cancer, which does have a sizeable body of evidence to suggest an effect on treatment decisions (resulting in fewer recommendations for chemotherapy), though not yet a clear effect on downstream outcomes.

At this point, physicians can, in many cases, rely on the prognostic value of molecular pathology tests, can share test results with patients, and discuss whether the test result indicates a better or worse than average prognosis. However, in most cases, physicians cannot be sure whether they should direct management plans based on the results. Although having accurate information about prognosis may be valued by patients independent of its effects on treatment planning or on survival and recurrence outcomes, this has yet to be demonstrated for the tests of interest.

Policymakers may request information and research that not only demonstrate the prognostic value of a test for cancer recurrence, but also evaluate the broader context of how the test fits into the overall plan of care and how information provided by the test changes a patient's long-term outcomes. Because molecular pathology tests for risk of cancer recurrence are relatively recent innovations in cancer care, it is reasonable for

policymakers to expect that their value may be better demonstrated over the next decade as the research base matures.

Limitations of the Comparative Effectiveness Review Process

We did not include studies focused on populations with advanced/metastatic cancer. The focus of this report is on whether the included tests are useful for prognosis as related to the risk of cancer recurrence. People with advanced/metastatic cancer would first have to achieve remission before recurrence is a possibility. Studies of people with advanced/metastatic cancer tend to focus on overall survival and typically do not provide information about the risk of cancer recurrence.

Also publication bias and selective reporting are potential limitations. Although we searched for unpublished studies and unpublished outcomes and did not find direct evidence of either of these biases, many of the included studies were published prior to the availability of registries that would allow for greater certainty in determining the potential for either type of bias.

Finally, although the r eview was focused om the Medicare population we did not find evidence specific to thulation. Many studies included participants from this age group and we did not find any evidence suggesting that the prognostic value of the tests varies with age.

Limitations of the Evidence Base

The evidence base was inadequate to draw conclusions for some of our questions or subquestions of interest. In particular, as described above, we found no direct evidence addressing our overarching question and insufficient evidence to determine whether modified decisions that result from prognostic testing lead to improved health outcomes. Further, we found scant evidence meeting our inclusion criteria regarding ALK translocation testing.

Although we found insufficient evidence to determine whether modified decisions that result from prognostic testing lead to improved health outcomes, studies of the use of Oncotype DX Breast reveal a pattern of less aggressive treatment recommendations as a result of using test information to inform decision-making (i.e., more recommendations for patients to have hormonal therapy alone than hormonal plus chemotherapy). We would expect this to improve quality of life and to decrease the costs of treatment, but we did not find empiric evidence to confirm this, and it might only hold true if recurrence and survival were either unchanged or were improved.

Many of the included studies had methodological limitations introducing some RoB. For example, most of them were observational studies assessing associations between test results and outcomes and are susceptible to potential confounding. To limit such bias, we only included studies for KQ 3 that adjusted for most or all standard prognostic factors. Also, we assessed potential selection bias and confounding in our RoB assessments—limiting our main data syntheses to studies with low or medium RoB.

We were also not able to address the prognostic value of the tests for the Medicare population due to a lack of data that was specific to that age group.

Future Research

We found no direct evidence of the impact of the information provided by these tests on downstream health outcomes such as patients' quality of life or survival. Thus, future research should focus on quality of life, survival, and other health outcomes. There is no information on the differential effects of the test by race or cancer subtype (e.g., ductal versus lobular in breast cancer) or location (e.g., proximal versus distal in CRC). As described in the results, the subpopulations that were represented in the studies varied in terms of stage, tumor type, and location in the case of CRC. Race and location have both been shown to be important predictors of the prognostic value of genetic markers in CRC.[152,153] Similar differences in prognostic value by subpopulations could be a factor in terms of *EGFR* and *KRAS* in the lung. There is thus a need to create an evidence base that replicates results in the same subpopulations, particularly in CRC and lung cancer.

As in many studies in the oncology field, the published literature uses a variety of specific definitions for outcomes such as recurrence and CSS, making comparison of effects across studies more difficult. Future research should take into account careful selection of the most appropriate endpoints, both in the context of the existing body of literature and the endpoints of most clinical relevance to doctors and patients.

Research on the prognostic value of molecular pathology tests, whether existing or novel, is limited by the lack of availability of biologic samples or detailed molecular pathology test result information from large population-based cohorts making assessment and generalizability of genetic prognostic tests difficult. Because many published studies used subsets of the same clinical trial populations, there is overlap in the sample of patients studied (e.g., three of the studies included for Oncotype DX in breast cancer report on the same 668 patients). There is a need to expand the research into independent populations and to incorporate collection of molecular pathology test results and/or biologic samples into the design of registry and prospective cohort studies. Although concerns may arise regarding privacy issues, these may be allayed by understanding that genetic alterations in the carcinomas, rather than those in germline DNA, are the focus of the research, and well-established ethical guidelines exist for handling and storing patient biospecimens.

Conclusions

We found modest evidence supporting added prognostic value (i.e., clinical validity), beyond traditional prognostic factors, for MammaPrint, Oncotype DX Breast, *KRAS* mutation testing for lung, *BRAF* mutation testing for CRC, *KRAS* mutation testing for CRC, and MSI for CRC for RR, CSS, and/or OS. For UroVysion, which is marketed as a diagnostic (not prognostic) test, limited evidence supported an association between test result and prognosis for RR. For the other included tests, evidence either did not support added prognostic value or we found no studies with sufficiently low RoB to support a conclusion about prognostic value.

We found no studies that directly addressed our overarching question (i.e., no studies directly assessed the impact of test use on downstream health outcomes to establish clinical utility). We attempted to construct an indirect chain of evidence to answer the overarching question, but evidence was generally insufficient to do so. Even for the tests

with good evidence supporting clinical validity, we found no evidence that using the test was related to improved outcomes for patients.

For impact of test use on treatment decisions, we found moderate SOE that Oncotype DX Breast leads to changes in decisions. One study of low or medium RoB found a significant impact of MammaPrint on treatment decisions, but evidence was insufficient to draw any firm conclusions, primarily because of unknown consistency and imprecision.

Many of the included tests are currently used to predict response to specific treatments, an aspect that was not evaluated in this report. A determination of whether the tests have clinical utility for predicting therapeutic response is beyond the scope of this review.

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Appendix A. Search Strategies

We conducted searches for relevant scientific literature using the following search strategies on 10/29/2012 and found 3,340 articles. We conducted an update literature using the same search terms and databases on 11/12/2013 with the following date limits: 10/29/2011 through 11/12/2013 to find more recently published articles. The update searches yielded a total of 1,233 citations, and after removing duplicates we added 468 new articles. The total number of unique sources found from the original and update searches and other sources such as hand searching and peer and public review comments was 3,850.

Table A1. PubMed update search strategies 11-11-2013

Search	Queries	Number of Citations
Urinary Bladder Cancer Search		
#1	Search "Urinary Bladder Neoplasms"[Mesh]	42283
#2	Search UroVysion	148
#3	Search IVDMIA OR "in vitro diagnostic multivariate index assay"	6
#4	Search #1 AND (#2 OR #3)	104
#5	Search "Biological Assay"[Mesh]	32692
#6	Search "Predictive Value of Tests"[Mesh]	133463
#7	Search "Proportional Hazards Models"[Mesh]	40213
#8	Search "Outcome and Process Assessment (Health Care)"[Mesh]	670462
#9	Search assay OR assays OR test OR tests	7676643
#10	Search #5 OR #6 OR #7 OR #8 OR #9	8058148
#11	Search #4 AND #10	101
#12	Search "Reproducibility of Results"[Mesh] OR “reproducibility of results”[all fields]	257185
#13	Search “Signal-to-Noise Ratio”[MeSH] OR “signal-to-noise ratio”[all fields]	16217
#14	Search “ROC Curve”[Mesh] OR "ROC curve"[All Fields] OR "receiver operating characteristic"[All Fields] OR “observer variation”[MeSH] OR “observer variation”[all fields]	71690
#15	Search “Sensitivity and Specificity”[Mesh] OR sensitiv*[Title/Abstract] OR "sensitivity and specificity"[All Fields] OR “analytic validity”[all fields]	1194419
#16	Search “Diagnostic Errors”[Mesh] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic[MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp] OR “accuracy”[All Fields] OR "diagnosis"[MeSH] "diagnostic accuracy”[All Fields] OR “precision”[All Fields] OR "diagnostic error*"[All Fields]	96343
#17	Search “Predictive Value of Tests”[Mesh] OR "probability"[MeSH] OR "probability"[All Fields] OR "likelihood"[All Fields] OR “false negative reactions”[MeSH] OR “false positive reactions”[MeSH] OR "predictive value of tests"[All Fields] OR "forecasting"[All Fields] OR "forecasting"[MeSH]	1212754
#18	Search #12 OR #13 OR #14 OR #15 OR #16 OR #17	2407314
#19	Search #4 AND (#10 OR #18)	103
#20	Search #4 AND (#10 OR #18) Humans	103
#21	Search #4 AND (#10 OR #18) Humans; English	97
#22	Search #4 AND (#10 OR #18) Humans; English; Adult: 19+ years	54
#23	Search #4 AND (#10 OR #18) Humans; English; Adult: 19+ years; Publication date from 1980/01/01	54
#24	Search #4 AND (#10 OR #18) Humans; English; Adult: 19+ years; Publication date from 2011/10/29	7
Breast Cancer Search		
#1	Search "Breast Neoplasms"[Mesh]	207319
#2	Search "oncotype DX" OR "21 gene recurrence score" OR "21 gene recurrence"	210

Search	Queries	Number of Citations
#3	Search “Mammaprint” OR “70 gene signature”	130
#4	Search IVDMIA OR "in vitro diagnostic multivariate index assay"	6
#5	Search #2 OR #3 OR #4	298
#6	Search #1 AND #5	213
#7	Search "Biological Assay"[Mesh]	32692
#8	Search "Predictive Value of Tests"[Mesh]	133463
#9	Search "Proportional Hazards Models"[Mesh]	40213
#10	Search "Outcome and Process Assessment (Health Care)"[Mesh]	670462
#11	Search assay OR assays OR test OR tests	7676643
#12	Search #7 OR #8 OR #9 OR #10 OR #11	8058148
#13	Search #6 AND #12	194
#14	Search "Reproducibility of Results"[Mesh] OR “reproducibility of results”[all fields]	257185
#15	Search “Signal-to-Noise Ratio”[MeSH] OR “signal-to-noise ratio”[all fields]	16217
#16	Search “ROC Curve”[Mesh] OR "ROC curve"[All Fields] OR "receiver operating characteristic"[All Fields] OR “observer variation”[MeSH] OR “observer variation”[all fields]	71690
#17	Search “Sensitivity and Specificity”[Mesh] OR sensitiv*[Title/Abstract] OR "sensitivity and specificity"[All Fields] OR “analytic validity”[all fields]	1194419
#18	Search “Diagnostic Errors”[Mesh] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic[MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp] OR “accuracy”[All Fields] OR "diagnosis"[MeSH] "diagnostic accuracy”[All Fields] OR “precision”[All Fields] OR "diagnostic error*"[All Fields]	96343
#19	Search “Predictive Value of Tests”[Mesh] OR "probability"[MeSH Terms] OR "probability"[All Fields] OR "likelihood"[All Fields] OR “false negative reactions”[MeSH] OR “false positive reactions”[MeSH] OR "predictive value of tests"[All Fields] OR "forecasting"[All Fields] OR "forecasting"[MeSH]	1212754
#20	Search #14 OR #15 OR #16 OR #17 OR #18 OR #19	2407314
#21	Search #6 AND (#12 OR #20)	202
#22	Search #6 AND (#12 OR #20) Humans	202
#23	Search #6 AND (#12 OR #20) Humans; English	195
#24	Search #6 AND (#12 OR #20) Humans; English; Adult: 19+ years	97
#25	Search #6 AND (#12 OR #20) Humans; English; Adult: 19+ years; Publication date from 1980/01/01	97
#26	Search #6 AND (#12 OR #20) Humans; English; Adult: 19+ years; Publication date from 2011/10/29	33
Colorectal Cancer Search		
#1	Search "Colorectal Neoplasms"[Mesh]	140842
#2	Search "Microsatellite Instability"[Mesh] OR "Microsatellite Instability"	5399
#3	Search MLH1 promoter methylation	627
#4	Search "KRAS protein, human" [Supplementary Concept] OR KRAS	8312
#5	Search "BRAF protein, human" [Supplementary Concept] OR BRAF	4522
#6	Search "Oncotype DX Colon" OR "21 gene recurrence score" OR "21 gene recurrence"	58
#7	Search IVDMIA OR "in vitro diagnostic multivariate index assay"	6
#8	Search #2 OR #3 OR #4 OR #5 OR #6 OR #7	16721
#9	Search #1 AND #8	4188
#10	Search "Biological Assay"[Mesh]	32692
#11	Search "Predictive Value of Tests"[Mesh]	133463
#12	Search "Proportional Hazards Models"[Mesh]	40213
#13	Search "Outcome and Process Assessment (Health Care)"[Mesh]	670462
#14	Search assay OR assays OR test OR tests	7676643
#15	Search #10 OR #11 OR #12 OR #13 OR #14	8058148
#16	Search #9 AND #15	2770
#17	Search "Reproducibility of Results"[Mesh] OR “reproducibility of results”[all fields]	257185
#18	Search “Signal-to-Noise Ratio”[MeSH] OR “signal-to-noise ratio”[all fields]	16217

Search	Queries	Number of Citations
#19	Search “ROC Curve”[Mesh] OR "ROC curve"[All Fields] OR "receiver operating characteristic"[All Fields] OR “observer variation”[MeSH] OR “observer variation”[all fields]	71690
#20	Search “Sensitivity and Specificity”[Mesh] OR sensitiv*[Title/Abstract] OR "sensitivity and specificity"[All Fields] OR “analytic validity”[all fields]	1194419
#21	Search “Diagnostic Errors”[Mesh] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic[MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp] OR “accuracy”[All Fields] OR "diagnosis"[MeSH] "diagnostic accuracy”[All Fields] OR “precision”[All Fields] OR "diagnostic error*"[All Fields]	96343
#22	Search “Predictive Value of Tests”[Mesh] OR "probability"[MeSH Terms] OR "probability"[All Fields] OR "likelihood"[All Fields] OR “false negative reactions”[MeSH] OR “false positive reactions”[MeSH] OR "predictive value of tests"[All Fields] OR "forecasting"[All Fields] OR "forecasting"[MeSH]	1212754
#23	Search #17 OR #18 OR #19 OR #20 OR #21 OR #22	2407314
#24	Search #9 AND (#15 OR #23)	2993
#25	Search #9 AND (#15 OR #23) Filters: Humans	2962
#26	Search #9 AND (#15 OR #23) Filters: Humans; English	2797
#27	Search #9 AND (#15 OR #23) Filters: Humans; English; Adult: 19+ years	1563
#28	Search #9 AND (#15 OR #23) Filters: Humans; English; Adult: 19+ years; Publication date from 1980/01/01	1563
#29	Search #9 AND (#15 OR #23) Filters: Humans; English; Adult: 19+ years; Publication date from 2011/10/29	345
Lung Cancer Search		
#1	Search "Lung Neoplasms"[Mesh]	166161
#2	Search "Carcinoma, Bronchogenic"[Mesh]	38075
#3	Search #1 OR #2	166161
#4	Search EML4-ALK fusion protein, human[Supplementary Concept]	143
#5	Search ALK	3768
#6	Search "EGFR protein, human"[Supplementary Concept] OR EGFR	26495
#7	Search "KRAS protein, human"[Supplementary Concept] OR KRAS	8312
#8	Search IVDMIA OR "in vitro diagnostic multivariate index assay"	6
#9	Search #4 OR #5 OR #6 OR #7 OR #8	36797
#10	Search #3 AND #9	4329
#11	Search "Biological Assay"[Mesh]	32692
#12	Search "Predictive Value of Tests"[Mesh]	133463
#13	Search "Proportional Hazards Models"[Mesh]	40213
#14	Search "Outcome and Process Assessment (Health Care)"[Mesh]	670462
#15	Search assay OR assays OR test OR tests	7676643
#16	Search #11 OR #12 OR #13 OR #14 OR #15	8058148
#17	Search #10 AND #16	2682
#18	Search "Reproducibility of Results"[Mesh] OR “reproducibility of results”[all fields]	257185
#19	Search “Signal-to-Noise Ratio”[MeSH] OR “signal-to-noise ratio”[all fields]	16217
#20	Search “ROC Curve”[Mesh] OR "ROC curve"[All Fields] OR "receiver operating characteristic"[All Fields] OR “observer variation”[MeSH] OR “observer variation”[all fields]	71690
#21	Search “Sensitivity and Specificity”[Mesh] OR sensitiv*[Title/Abstract] OR "sensitivity and specificity"[All Fields] OR “analytic validity”[all fields]	1194419
#22	Search “Diagnostic Errors”[Mesh] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic[MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp] OR “accuracy”[All Fields] OR "diagnosis"[MeSH] "diagnostic accuracy”[All Fields] OR “precision”[All Fields] OR "diagnostic error*"[All Fields]	96343
#23	Search “Predictive Value of Tests”[Mesh] OR "probability"[MeSH Terms] OR "probability"[All Fields] OR "likelihood"[All Fields] OR “false negative reactions”[MeSH] OR “false positive reactions”[MeSH] OR "predictive value of tests"[All Fields] OR "forecasting"[All Fields] OR "forecasting"[MeSH]	1212754

Search	Queries	Number of Citations
#24	Search #18 OR #19 OR #20 OR #21 OR #22 OR #23	2407314
#25	Search #10 AND (#16 OR #24)	2992
#26	Search #10 AND (#16 OR #24) Filters: Humans	2912
#27	Search #10 AND (#16 OR #24) Humans; English	2696
#28	Search #10 AND (#16 OR #24) Humans; English; Adult: 19+ years	1292
#29	Search #10 AND (#16 OR #24) Humans; English; Adult: 19+ years; Publication date from 1980/01/01	1292
#30	Search #10 AND (#16 OR #24) Humans; English; Adult: 19+ years; Publication date from 2011/10/29	423

Table A2. Embase search strategies update 11-12-2013

Search	Queries	Number of Citations
Urinary Bladder Cancer Search		
#1	'bladder tumor'/exp AND ([embase]/lim OR [embase classic]/lim)	46,402
#2	urovysion AND ([embase]/lim OR [embase classic]/lim)	257
#3	ivdmia OR 'in vitro diagnostic multivariate index assay' AND ([embase]/lim OR [embase classic]/lim)	13
#4	#1 AND (#2 OR #3)	170
#5	'biological assay'/exp AND ([embase]/lim OR [embase classic]/lim)	27,120
#6	'predictive value of tests'/exp AND ([embase]/lim OR [embase classic]/lim)	36,618
#7	'proportional hazards models'/exp AND ([embase]/lim OR [embase classic]/lim)	31,586
#8	'treatment outcome'/exp AND ([embase]/lim OR [embase classic]/lim)	770,815
#9	'assay'/de OR assay OR assays OR test OR tests AND ([embase]/lim OR [embase classic]/lim)	2,791,862
#10	#5 OR #6 OR #7 OR #8 OR #9	3,455,670
#11	#4 AND #10	124
#12	'reproducibility of results'/exp OR 'reproducibility of results' AND ([embase]/lim OR [embase classic]/lim)	58,613
#13	'signal-to-noise ratio'/exp OR 'signal-to-noise ratio' AND ([embase]/lim OR [embase classic]/lim)	21,815
#14	'roc curve'/exp OR 'roc curve' OR 'receiver operating characteristic'/exp OR 'receiver operating characteristic' OR 'observer variation'/exp OR 'observer variation' AND ([embase]/lim OR [embase classic]/lim)	42,593
#15	'sensitivity and specificity'/exp OR 'sensitivity and specificity' OR 'sensitivity':ti OR 'sensitivity':ab OR 'analytic validity' AND ([embase]/lim OR [embase classic]/lim)	553,407
#16	'diagnostic errors'/exp OR 'diagnostic errors' OR 'diagnosis':ti OR 'diagnosis':ab OR 'diagnostic accuracy'/exp OR 'diagnostic accuracy' OR 'precision'/exp OR 'precision' AND ([embase]/lim OR [embase classic]/lim)	1,266,288
#17	'probability'/exp OR probability OR likelihood OR 'false negative reactions'/exp OR 'false negative reactions' OR 'false positive reactions'/exp OR 'false positive reactions' OR 'predictive value of tests'/exp OR 'predictive value of tests' OR 'forecasting'/exp OR forecasting AND ([embase]/lim OR [embase classic]/lim)	284,237
#18	#12 OR #13 OR #14 OR #15 OR #16 OR #17	1,942,881
#19	#4 AND (#10 OR #18)	158
#20	#19 AND ([adult]/lim OR [aged]/lim) AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim) AND [1980-2012]/py	33
#21	#19 AND ([adult]/lim OR [aged]/lim) AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim) AND [1980-2012]/py AND [29-10-2011]/sd	5
Breast Cancer Search		
#1	'breast cancer'/exp AND ([embase]/lim OR [embase classic]/lim)	269,829
#2	'oncotype dx' OR '21 gene recurrence score' OR '21 gene recurrence' AND	606

Search	Queries	Number of Citations
	([embase]/lim OR [embase classic]/lim)	
#3	'mammaprint' OR '70 gene signature' AND ([embase]/lim OR [embase classic]/lim)	341
#4	ivdmia OR 'in vitro diagnostic multivariate index assay' AND ([embase]/lim OR [embase classic]/lim)	13
#5	#2 OR #3 OR #4	825
#6	#1 AND #5	762
#7	'biological assay'/exp AND ([embase]/lim OR [embase classic]/lim)	27,120
#8	'predictive value of tests'/exp AND ([embase]/lim OR [embase classic]/lim)	36,618
#9	'proportional hazards models'/exp AND ([embase]/lim OR [embase classic]/lim)	31,586
#10	'treatment outcome'/exp AND ([embase]/lim OR [embase classic]/lim)	770,815
#11	'assay' OR 'assay'/exp OR assay OR assays OR test OR tests AND ([embase]/lim OR [embase classic]/lim)	2,791,862
#12	#7 OR #8 OR #9 OR #10 OR #11	3,455,570
#13	#6 AND #12	551
#14	'reproducibility of results'/exp OR 'reproducibility of results' AND ([embase]/lim OR [embase classic]/lim)	58,613
#15	'signal-to-noise ratio'/exp OR 'signal-to-noise ratio' AND ([embase]/lim OR [embase classic]/lim)	21,815
#16	'roc curve'/exp OR 'roc curve' OR 'receiver operating characteristic'/exp OR 'receiver operating characteristic' OR 'observer variation'/exp OR 'observer variation' AND ([embase]/lim OR [embase classic]/lim)	42,593
#17	'sensitivity and specificity'/exp OR 'sensitivity and specificity' OR 'sensitivity':ti OR 'sensitivity':ab OR 'analytic validity' AND ([embase]/lim OR [embase classic]/lim)	563,407
#18	'diagnostic errors'/exp OR 'diagnostic errors' OR 'diagnosis':ti OR 'diagnosis':ab OR 'diagnostic accuracy'/exp OR 'diagnostic accuracy' OR 'precision'/exp OR 'precision' AND ([embase]/lim OR [embase classic]/lim)	1,266,228
#19	'probability' OR 'probability'/exp OR probability OR likelihood OR 'false negative reactions'/exp OR 'false negative reactions' OR 'false positive reactions'/exp OR 'false positive reactions' OR 'predictive value of tests'/exp OR 'predictive value of tests' OR 'forecasting' OR 'forecasting'/exp OR forecasting AND ([embase]/lim OR [embase classic]/lim)	284,237
#20	#14 OR #15 OR #16 OR #17 OR #18 OR #19	1,942,881
#21	#6 AND (#12 OR #20)	610
#22	#21 AND ([adult]/lim OR [aged]/lim) AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim) AND [1980-2012]/py	68
#23	#21 AND ([adult]/lim OR [aged]/lim) AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim) AND [1980-2012]/py AND [29-10-2011]/sd	22
Colorectal Cancer Search		
#1	'colorectal cancer'/exp AND ([embase]/lim OR [embase classic]/lim)	75,215
#2	'microsatellite instability'/exp OR 'microsatellite instability' AND ([embase]/lim OR [embase classic]/lim)	6,746
#3	mlh1 AND ('promoter'/exp OR promoter) AND ('methylation'/exp OR methylation) AND ([embase]/lim OR [embase classic]/lim)	275
#4	kras AND ([embase]/lim OR [embase classic]/lim)	7,176
#5	braf AND ([embase]/lim OR [embase classic]/lim)	6,862
#6	'oncotype dx colon' OR '21 gene recurrence score' OR '21 gene recurrence' AND ([embase]/lim OR [embase classic]/lim)	135
#7	ivdmia OR 'in vitro diagnostic multivariate index assay' AND ([embase]/lim OR [embase classic]/lim)	13
#8	#2 OR #3 OR #4 OR #5 OR #6 OR #7	18,195
#9	#1 AND #8	4,955
#10	'biological assay'/exp AND ([embase]/lim OR [embase classic]/lim)	27,120
#11	'predictive value of tests'/exp AND ([embase]/lim OR [embase classic]/lim)	36,618

Search	Queries	Number of Citations
#12	'proportional hazards models'/exp AND ([embase]/lim OR [embase classic]/lim)	31,586
#13	'treatment outcome'/exp AND ([embase]/lim OR [embase classic]/lim)	770,815
#14	'assay' OR 'assay'/exp OR assay OR assays OR test OR tests AND ([embase]/lim OR [embase classic]/lim)	2,791,862
#15	#10 OR #11 OR #12 OR #13 OR #14	3,455,670
#16	#9 AND #15	1,455
#17	'reproducibility of results'/exp OR 'reproducibility of results' AND ([embase]/lim OR [embase classic]/lim)	58,613
#18	'signal-to-noise ratio'/exp OR 'signal-to-noise ratio' AND ([embase]/lim OR [embase classic]/lim)	21,815
#19	'roc curve'/exp OR 'roc curve' OR 'receiver operating characteristic'/exp OR 'receiver operating characteristic' OR 'observer variation'/exp OR 'observer variation' AND ([embase]/lim OR [embase classic]/lim)	42,593
#20	'sensitivity and specificity'/exp OR 'sensitivity and specificity' OR 'sensitivity':ti OR 'sensitivity':ab OR 'analytic validity' AND ([embase]/lim OR [embase classic]/lim)	553,407
#21	'diagnostic errors'/exp OR 'diagnostic errors' OR 'diagnosis':ti OR 'diagnosis':ab OR 'diagnostic accuracy'/exp OR 'diagnostic accuracy' OR 'precision'/exp OR 'precision' AND ([embase]/lim OR [embase classic]/lim)	1,266,228
#22	'probability' OR 'probability'/exp OR probability OR likelihood OR 'false negative reactions'/exp OR 'false negative reactions' OR 'false positive reactions'/exp OR 'false positive reactions' OR 'predictive value of tests'/exp OR 'predictive value of tests' OR 'forecasting' OR 'forecasting'/exp OR forecasting AND ([embase]/lim OR [embase classic]/lim)	284,237
#23	#17 OR #18 OR #19 OR #20 OR #21 OR #22	1,942,881
#24	#9 AND (#15 OR #23)	2,108
#25	#24 AND ([adult]/lim OR [aged]/lim) AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim) AND [1980-2012]/py	446
#26	#24 AND ([adult]/lim OR [aged]/lim) AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim) AND [1980-2012]/py AND [29-10-2011]/sd	100
Lung Cancer Search		
#1	'lung cancer'/exp AND ([embase]/lim OR [embase classic]/lim)	185,331
#2	'lung carcinoma'/exp AND ([embase]/lim OR [embase classic]/lim)	95,316
#3	#1 OR #2	185,331
#4	'eml4-alk' AND ([embase]/lim OR [embase classic]/lim)	592
#5	alk AND ([embase]/lim OR [embase classic]/lim)	6,136
#6	egfr AND ([embase]/lim OR [embase classic]/lim)	37,705
#7	kras AND ([embase]/lim OR [embase classic]/lim)	7,176
#8	ivdmia OR 'in vitro diagnostic multivariate index assay' AND ([embase]/lim OR [embase classic]/lim)	13
#9	#4 OR #5 OR #6 OR #7 OR #8	47,551
#10	#3 AND #9	8,953
#11	'biological assay'/exp AND ([embase]/lim OR [embase classic]/lim)	27,120
#12	'predictive value of tests'/exp AND ([embase]/lim OR [embase classic]/lim)	36,618
#13	'proportional hazards models'/exp AND ([embase]/lim OR [embase classic]/lim)	31,586
#14	'treatment outcome'/exp AND ([embase]/lim OR [embase classic]/lim)	770,815
#15	'assay' OR 'assay'/exp OR assay OR assays OR test OR tests AND ([embase]/lim OR [embase classic]/lim)	2,791,862
#16	#11 OR #12 OR #13 OR #14 OR #15	3,455,670
#17	#10 AND #16	2,799
#18	'reproducibility of results'/exp OR 'reproducibility of results' AND ([embase]/lim OR [embase classic]/lim)	58,613
#19	'signal-to-noise ratio'/exp OR 'signal-to-noise ratio' AND ([embase]/lim OR [embase classic]/lim)	21,815

Search	Queries	Number of Citations
#20	'roc curve'/exp OR 'roc curve' OR 'receiver operating characteristic'/exp OR 'receiver operating characteristic' OR 'observer variation'/exp OR 'observer variation' AND ([embase]/lim OR [embase classic]/lim)	42,593
#21	'sensitivity and specificity'/exp OR 'sensitivity and specificity' OR 'sensitivity':ti OR 'sensitivity':ab OR 'analytic validity' AND ([embase]/lim OR [embase classic]/lim)	553,407
#22	'diagnostic errors'/exp OR 'diagnostic errors' OR 'diagnosis':ti OR 'diagnosis':ab OR 'diagnostic accuracy'/exp OR 'diagnostic accuracy' OR 'precision'/exp OR 'precision' AND ([embase]/lim OR [embase classic]/lim)	1,266,228
#23	'probability' OR 'probability'/exp OR probability OR likelihood OR 'false negative reactions'/exp OR 'false negative reactions' OR 'false positive reactions'/exp OR 'false positive reactions' OR 'predictive value of tests'/exp OR 'predictive value of tests' OR 'forecasting' OR 'forecasting'/exp OR forecasting AND ([embase]/lim OR [embase classic]/lim)	284,237
#24	#18 OR #19 OR #20 OR #21 OR #22 OR #23	1,942,881
#25	#10 AND (#16 OR #24)	4,029
#26	#25 AND ([adult]/lim OR [aged]/lim) AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim) AND [1980-2012]/py	756
#27	#25 AND ([adult]/lim OR [aged]/lim) AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim) AND [1980-2012]/py AND [29-10-2011]/sd	241

Table A3. Cochrane search strategies update 11-12-2013

Search	Queries	Number of Citations
Urinary Bladder Cancer Search		
#1	MeSH descriptor: [Urinary Bladder Neoplasms] explode all trees	988
#2	urovysion	2
#3	ivdmia	1
#4	"in vitro multivariate index assay"	0
#5	#1 and (#2 or #3 or #4)	2
#6	MeSH descriptor: [Biological Assay] explode all trees	153
#7	MeSH descriptor: [Predictive Value of Tests] explode all trees	5420
#8	MeSH descriptor: [Proportional Hazards Models] explode all trees	3086
#9	MeSH descriptor: [Outcome and Process Assessment (Health Care)] explode all trees	89878
#10	assay	11865
#11	assays	11865
#12	test	149897
#13	tests	149897
#14	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13	225622
#15	MeSH descriptor: [Reproducibility of Results] explode all trees	8399
#16	"reproducibility of results"	8720
#17	MeSH descriptor: [Signal-To-Noise Ratio] explode all trees	4
#18	"signal-to-noise ratio"	154
#19	MeSH descriptor: [ROC Curve] explode all trees	939
#20	"ROC Curve"	1224
#21	"receiver operating characteristic"	1253
#22	MeSH descriptor: [Observer Variation] explode all trees	1601
#23	“observer variation”	1796
#24	MeSH descriptor: [Sensitivity and Specificity] explode all trees	14453
#25	sensitivity:ti (Word variations have been searched)	2853
#26	sensitivity:ab (Word variations have been searched)	15946
#27	"sensitivity and specificity"	11631

Search	Queries	Number of Citations
#28	“analytic validity”	9
#29	MeSH descriptor: [Diagnostic Errors] explode all trees	2444
#30	diagnos*:ti,ab	35756
#31	MeSH descriptor: [Diagnosis] this term only	232499
#32	MeSH descriptor: [Diagnosis, Differential] this term only	1401
#33	Any MeSH descriptor with qualifier(s): [Diagnosis - DI]	35316
#34	accuracy	10492
#35	MeSH descriptor: [Diagnosis] explode all trees	232499
#36	diagnostic accuracy	4494
#37	precision	3052
#38	"diagnostic error*"	312
#39	MeSH descriptor: [Predictive Value of Tests] explode all trees	5420
#40	MeSH descriptor: [Probability] explode all trees	34522
#41	probability	12210
#42	likelihood	6636
#43	MeSH descriptor: [False Negative Reactions] explode all trees	323
#44	MeSH descriptor: [False Positive Reactions] explode all trees	490
#45	"predictive value of test*"	5548
#46	forecasting	624
#47	MeSH descriptor: [Forecasting] explode all trees	456
#48	#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47	289183
#49	#5 and (#14 or #48)	2
#50	#5 and (#14 or #48) from 1980	2
#51	#5 and (#14 or #48) from 2011	0
Breast Cancer Search		
#1	MeSH descriptor: [Breast Neoplasms] explode all trees	8030
#2	"oncotype DX"	13
#3	"21 gene recurrence score"	11
#4	"21 gene recurrence"	11
#5	Mammaprint	10
#6	"70 gene signature"	3
#7	ivdmia	1
#8	"in vitro multivariate index assay"	0
#9	#1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)	30
#10	MeSH descriptor: [Biological Assay] explode all trees	153
#11	MeSH descriptor: [Predictive Value of Tests] explode all trees	5420
#12	MeSH descriptor: [Proportional Hazards Models] explode all trees	3086
#13	MeSH descriptor: [Outcome and Process Assessment (Health Care)] explode all trees	89878
#14	assay	11865
#15	assays	11865
#16	test	149897
#17	tests	149897
#18	#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17	225622
#19	MeSH descriptor: [Reproducibility of Results] explode all trees	8399
#20	"reproducibility of results"	8720
#21	MeSH descriptor: [Signal-To-Noise Ratio] explode all trees	4
#22	"signal-to-noise ratio"	154
#23	MeSH descriptor: [ROC Curve] explode all trees	939
#24	"ROC Curve"	1224
#25	"receiver operating characteristic"	1253
#26	MeSH descriptor: [Observer Variation] explode all trees	1601

Search	Queries	Number of Citations
#27	“observer variation”	1796
#28	MeSH descriptor: [Sensitivity and Specificity] explode all trees	14453
#29	sensitivity:ti (Word variations have been searched)	2853
#30	sensitivity:ab (Word variations have been searched)	15946
#31	"sensitivity and specificity"	11631
#32	“analytic validity”	9
#33	MeSH descriptor: [Diagnostic Errors] explode all trees	2444
#34	diagnos*:ti,ab	35756
#35	MeSH descriptor: [Diagnosis] this term only	232499
#36	MeSH descriptor: [Diagnosis, Differential] this term only	1401
#37	Any MeSH descriptor with qualifier(s): [Diagnosis - DI]	35316
#38	accuracy	10492
#39	MeSH descriptor: [Diagnosis] explode all trees	232499
#40	diagnostic accuracy	4494
#41	precision	3052
#42	"diagnostic error*"	312
#43	MeSH descriptor: [Predictive Value of Tests] explode all trees	5420
#44	MeSH descriptor: [Probability] explode all trees	34522
#45	probability	12210
#46	likelihood	6636
#47	MeSH descriptor: [False Negative Reactions] explode all trees	323
#48	MeSH descriptor: [False Positive Reactions] explode all trees	490
#49	"predictive value of test*"	5548
#50	forecasting	624
#51	MeSH descriptor: [Forecasting] explode all trees	456
#52	#19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51	289183
#53	#9 and (#18 or #52)	29
#54	#9 and (#18 or #52) from 1980	29
#55	#9 and (#18 or #52) from 2011	16
Colorectal Cancer Search		
#1	MeSH descriptor: [Colorectal Neoplasms] explode all trees	8030
#2	MeSH descriptor: [Microsatellite Instability] explode all trees	25
#3	"Microsatellite Instability"	59
#4	MLH1 promoter methylation	3
#5	KRAS protein, human	90
#6	KRAS	140
#7	BRAF protein, human	41
#8	"Oncotype DX Colon"	0
#9	"21 gene recurrence score"	11
#10	"21 gene recurrence"	11
#11	ivdmia	1
#12	"in vitro multivariate index assay"	0
#13	#1 and (#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12)	14
#14	MeSH descriptor: [Biological Assay] explode all trees	153
#15	MeSH descriptor: [Predictive Value of Tests] explode all trees	5420
#16	MeSH descriptor: [Proportional Hazards Models] explode all trees	3086
#17	MeSH descriptor: [Outcome and Process Assessment (Health Care)] explode all trees	89878
#18	assay	11865
#19	assays	11865
#20	test	149897
#21	tests	149897

Search	Queries	Number of Citations
#22	#14 or #15 or #16 or #17 or #18 or #19 or #20 or #21	225622
#23	MeSH descriptor: [Reproducibility of Results] explode all trees	8399
#24	"reproducibility of results"	8720
#25	MeSH descriptor: [Signal-To-Noise Ratio] explode all trees	4
#26	"signal-to-noise ratio"	154
#27	MeSH descriptor: [ROC Curve] explode all trees	939
#28	"ROC Curve"	1224
#29	"receiver operating characteristic"	1253
#30	MeSH descriptor: [Observer Variation] explode all trees	1601
#31	“observer variation”	1796
#32	MeSH descriptor: [Sensitivity and Specificity] explode all trees	14453
#33	sensitivity:ti (Word variations have been searched)	2853
#34	sensitivity:ab (Word variations have been searched)	15946
#35	"sensitivity and specificity"	11631
#36	“analytic validity”	9
#37	MeSH descriptor: [Diagnostic Errors] explode all trees	2444
#38	diagnos*:ti,ab	35756
#39	MeSH descriptor: [Diagnosis] this term only	232499
#40	MeSH descriptor: [Diagnosis, Differential] this term only	1401
#41	Any MeSH descriptor with qualifier(s): [Diagnosis - DI]	35316
#42	accuracy	10492
#43	MeSH descriptor: [Diagnosis] explode all trees	232499
#44	diagnostic accuracy	4494
#45	precision	3052
#46	"diagnostic error*"	312
#47	MeSH descriptor: [Predictive Value of Tests] explode all trees	5420
#48	MeSH descriptor: [Probability] explode all trees	34522
#49	probability	12210
#50	likelihood	6636
#51	MeSH descriptor: [False Negative Reactions] explode all trees	323
#52	MeSH descriptor: [False Positive Reactions] explode all trees	490
#53	"predictive value of test*"	5548
#54	forecasting	624
#55	MeSH descriptor: [Forecasting] explode all trees	456
#56	#23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55	289183
#57	#13 and (#22 or #56)	14
#58	#13 and (#22 or #56) from 1980	14
#59	#13 and (#22 or #56) from 2011	7
Lung Cancer Search		
#1	MeSH descriptor: [Lung Neoplasms] explode all trees	4548
#2	MeSH descriptor: [Carcinoma, Bronchogenic] explode all trees	2388
#3	#1 or #2	4548
#4	EML4-ALK fusion protein, human	0
#5	ALK	125
#6	EGFR protein, human	221
#7	EGFR	655
#8	KRAS protein, human	90
#9	KRAS	140
#10	ivdmia	1
#11	"in vitro multivariate index assay"	0
#12	#3 and (#4 or #5 or #6 or #8 or #9 or #10 or #11)	75
#13	MeSH descriptor: [Biological Assay] explode all trees	153

Search	Queries	Number of Citations
#14	MeSH descriptor: [Predictive Value of Tests] explode all trees	5420
#15	MeSH descriptor: [Proportional Hazards Models] explode all trees	3086
#16	MeSH descriptor: [Outcome and Process Assessment (Health Care)] explode all trees	89878
#17	assay	11865
#18	assays	11865
#19	test	149897
#20	tests	149897
#21	#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20	225622
#22	MeSH descriptor: [Reproducibility of Results] explode all trees	8399
#23	"reproducibility of results"	8720
#24	MeSH descriptor: [Signal-To-Noise Ratio] explode all trees	4
#25	"signal-to-noise ratio"	154
#26	MeSH descriptor: [ROC Curve] explode all trees	939
#27	"ROC Curve"	1224
#28	"receiver operating characteristic"	1253
#29	MeSH descriptor: [Observer Variation] explode all trees	1601
#30	“observer variation”	1796
#31	MeSH descriptor: [Sensitivity and Specificity] explode all trees	14453
#32	sensitivity:ti (Word variations have been searched)	2853
#33	sensitivity:ab (Word variations have been searched)	15946
#34	"sensitivity and specificity"	11631
#35	“analytic validity”	9
#36	MeSH descriptor: [Diagnostic Errors] explode all trees	2444
#37	diagnos*:ti,ab	35756
#38	MeSH descriptor: [Diagnosis] this term only	232499
#39	MeSH descriptor: [Diagnosis, Differential] this term only	1401
#40	Any MeSH descriptor with qualifier(s): [Diagnosis - DI]	35316
#41	accuracy	10492
#42	MeSH descriptor: [Diagnosis] explode all trees	232499
#43	diagnostic accuracy	4494
#44	precision	3052
#45	"diagnostic error*"	312
#46	MeSH descriptor: [Predictive Value of Tests] explode all trees	5420
#47	MeSH descriptor: [Probability] explode all trees	34522
#48	probability	12210
#49	likelihood	6636
#50	MeSH descriptor: [False Negative Reactions] explode all trees	323
#51	MeSH descriptor: [False Positive Reactions] explode all trees	490
#52	"predictive value of test*"	5548
#53	forecasting	624
#54	MeSH descriptor: [Forecasting] explode all trees	456
#55	#22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54	289183
#56	#12 and (#21 or #55)	60
#57	#12 and (#21 or #55) from 1980	60
#58	#12 and (#21 or #55) from 2011	34

Table A4. PubMed search strategies 10-29-2012

Search	Queries	Number of Citations
Urinary Bladder Cancer Search		
#1	Search "Urinary Bladder Neoplasms"[Mesh]	40721
#2	Search UroVysion	127
#3	Search IVDMIA OR "in vitro diagnostic multivariate index assay"	138
#4	Search #1 AND (#2 OR #3)	98
#5	Search "Biological Assay"[Mesh]	31814
#6	Search "Predictive Value of Tests"[Mesh]	123188
#7	Search "Proportional Hazards Models"[Mesh]	35131
#8	Search "Outcome and Process Assessment (Health Care)"[Mesh]	616326
#9	Search assay OR assays OR test OR tests	7254565
#10	Search #5 OR #6 OR #7 OR #8 OR #9	7608298
#11	Search #4 AND #10	95
#12	Search "Reproducibility of Results"[Mesh] OR “reproducibility of results”[all fields]	237807
#13	Search “Signal-to-Noise Ratio”[MeSH] OR “signal-to-noise ratio”[all fields]	14372
#14	Search “ROC Curve”[Mesh] OR "ROC curve"[All Fields] OR "receiver operating characteristic"[All Fields] OR “observer variation”[MeSH] OR “observer variation”[all fields]	63708
#15	Search “Sensitivity and Specificity”[Mesh] OR sensitiv*[Title/Abstract] OR "sensitivity and specificity"[All Fields] OR “analytic validity”[all fields]	1119176
#16	Search “Diagnostic Errors”[Mesh] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic[MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp] OR “accuracy”[All Fields] OR "diagnosis"[MeSH] "diagnostic accuracy”[All Fields] OR “precision”[All Fields] OR "diagnostic error*"[All Fields]	87894
#17	Search “Predictive Value of Tests”[Mesh] OR "probability"[MeSH] OR "probability"[All Fields] OR "likelihood"[All Fields] OR “false negative reactions”[MeSH] OR “false positive reactions”[MeSH] OR "predictive value of tests"[All Fields] OR "forecasting"[All Fields] OR "forecasting"[MeSH]	1129894
#18	Search #12 OR #13 OR #14 OR #15 OR #16 OR #17	2249689
#19	Search #4 AND (#10 OR #18)	97
#20	Search #4 AND (#10 OR #18) Humans	97
#21	Search #4 AND (#10 OR #18) Humans; English	92
#22	Search #4 AND (#10 OR #18) Humans; English; Adult: 19+ years	51
#23	Search #4 AND (#10 OR #18) Humans; English; Adult: 19+ years; Publication date from 1980/01/01	51
Breast Cancer Search		
#1	Search "Breast Neoplasms"[Mesh]	196562
#2	Search "oncotype DX" OR "21 gene recurrence score" OR "21 gene recurrence"	158
#3	Search “Mammaprint” OR “70 gene signature”	101
#4	Search IVDMIA OR "in vitro diagnostic multivariate index assay"	138
#5	Search #2 OR #3 OR #4	358
#6	Search #1 AND #5	178
#7	Search "Biological Assay"[Mesh]	31814
#8	Search "Predictive Value of Tests"[Mesh]	123188
#9	Search "Proportional Hazards Models"[Mesh]	35131
#10	Search "Outcome and Process Assessment (Health Care)"[Mesh]	616326
#11	Search assay OR assays OR test OR tests	7254565
#12	Search #7 OR #8 OR #9 OR #10 OR #11	7588075
#13	Search #6 AND #12	164
#14	Search "Reproducibility of Results"[Mesh] OR “reproducibility of results”[all fields]	237807
#15	Search “Signal-to-Noise Ratio”[MeSH] OR “signal-to-noise ratio”[all fields]	14372
#16	Search “ROC Curve”[Mesh] OR "ROC curve"[All Fields] OR "receiver operating characteristic"[All Fields] OR “observer variation”[MeSH] OR	63708

Search	Queries	Number of Citations
	“observer variation”[all fields]	
#17	Search “Sensitivity and Specificity”[Mesh] OR sensitiv*[Title/Abstract] OR "sensitivity and specificity"[All Fields] OR “analytic validity”[all fields]	1119176
#18	Search “Diagnostic Errors”[Mesh] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic[MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp] OR “accuracy”[All Fields] OR "diagnosis"[MeSH] "diagnostic accuracy”[All Fields] OR “precision”[All Fields] OR "diagnostic error*"[All Fields]	87894
#19	Search “Predictive Value of Tests”[Mesh] OR "probability"[MeSH Terms] OR "probability"[All Fields] OR "likelihood"[All Fields] OR “false negative reactions”[MeSH] OR “false positive reactions”[MeSH] OR "predictive value of tests"[All Fields] OR "forecasting"[All Fields] OR "forecasting"[MeSH]	1129894
#20	Search #14 OR #15 OR #16 OR #17 OR #18 OR #19	2249689
#21	Search #6 AND (#12 OR #20)	170
#22	Search #6 AND (#12 OR #20) Humans	170
#23	Search #6 AND (#12 OR #20) Humans; English	166
#24	Search #6 AND (#12 OR #20) Humans; English; Adult: 19+ years	84
#25	Search #6 AND (#12 OR #20) Humans; English; Adult: 19+ years; Publication date from 1980/01/01	84
Colorectal Cancer Search		
#1	Search "Colorectal Neoplasms"[Mesh]	133525
#2	Search "Microsatellite Instability"[Mesh] OR "Microsatellite Instability"	5029
#3	Search MLH1 promoter methylation	581
#4	Search "KRAS protein, human" [Supplementary Concept] OR KRAS	3263
#5	Search "BRAF protein, human" [Supplementary Concept] OR BRAF	3374
#6	Search "Oncotype DX Colon" OR "21 gene recurrence score" OR "21 gene recurrence"	46
#7	Search IVDMIA OR "in vitro diagnostic multivariate index assay"	138
#8	Search #2 OR #3 OR #4 OR #5 OR #6 OR #7	10733
#9	Search #1 AND #8	3532
#10	Search "Biological Assay"[Mesh]	31814
#11	Search "Predictive Value of Tests"[Mesh]	123188
#12	Search "Proportional Hazards Models"[Mesh]	35131
#13	Search "Outcome and Process Assessment (Health Care)"[Mesh]	616326
#14	Search assay OR assays OR test OR tests	7254565
#15	Search #10 OR #11 OR #12 OR #13 OR #14	7608298
#16	Search #9 AND #15	2315
#17	Search "Reproducibility of Results"[Mesh] OR “reproducibility of results”[all fields]	237807
#18	Search “Signal-to-Noise Ratio”[MeSH] OR “signal-to-noise ratio”[all fields]	14372
#19	Search “ROC Curve”[Mesh] OR "ROC curve"[All Fields] OR "receiver operating characteristic"[All Fields] OR “observer variation”[MeSH] OR “observer variation”[all fields]	63708
#20	Search “Sensitivity and Specificity”[Mesh] OR sensitiv*[Title/Abstract] OR "sensitivity and specificity"[All Fields] OR “analytic validity”[all fields]	1119176
#21	Search “Diagnostic Errors”[Mesh] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic[MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp] OR “accuracy”[All Fields] OR "diagnosis"[MeSH] "diagnostic accuracy”[All Fields] OR “precision”[All Fields] OR "diagnostic error*"[All Fields]	87894
#22	Search “Predictive Value of Tests”[Mesh] OR "probability"[MeSH Terms] OR "probability"[All Fields] OR "likelihood"[All Fields] OR “false negative reactions”[MeSH] OR “false positive reactions”[MeSH] OR "predictive value of tests"[All Fields] OR "forecasting"[All Fields] OR "forecasting"[MeSH]	1129894
#23	Search #17 OR #18 OR #19 OR #20 OR #21 OR #22	2249689
#24	Search #9 AND (#15 OR #23)	2513
#25	Search #9 AND (#15 OR #23) Filters: Humans	2492
#26	Search #9 AND (#15 OR #23) Filters: Humans; English	2363

Search	Queries	Number of Citations
#27	Search #9 AND (#15 OR #23) Filters: Humans; English; Adult: 19+ years	1338
#28	Search #9 AND (#15 OR #23) Filters: Humans; English; Adult: 19+ years; Publication date from 1980/01/01	1338
Lung Cancer Search		
#1	Search "Lung Neoplasms"[Mesh]	158827
#2	Search "Carcinoma, Bronchogenic"[Mesh]	35282
#3	Search #1 OR #2	158827
#4	Search EML4-ALK fusion protein, human[Supplementary Concept]	90
#5	Search ALK	3208
#6	Search "EGFR protein, human"[Supplementary Concept] OR EGFR	22440
#7	Search "KRAS protein, human"[Supplementary Concept] OR KRAS	3263
#8	Search IVDMIA OR "in vitro diagnostic multivariate index assay"	138
#9	Search #4 OR #5 OR #6 OR #7 OR #8	27905
#10	Search #3 AND #9	3380
#11	Search "Biological Assay"[Mesh]	31814
#12	Search "Predictive Value of Tests"[Mesh]	123188
#13	Search "Proportional Hazards Models"[Mesh]	35131
#14	Search "Outcome and Process Assessment (Health Care)"[Mesh]	616326
#15	Search assay OR assays OR test OR tests	7254565
#16	Search #11 OR #12 OR #13 OR #14 OR #15	7608298
#17	Search #10 AND #16	2081
#18	Search "Reproducibility of Results"[Mesh] OR “reproducibility of results”[all fields]	237807
#19	Search “Signal-to-Noise Ratio”[MeSH] OR “signal-to-noise ratio”[all fields]	14372
#20	Search “ROC Curve”[Mesh] OR "ROC curve"[All Fields] OR "receiver operating characteristic"[All Fields] OR “observer variation”[MeSH] OR “observer variation”[all fields]	63708
#21	Search “Sensitivity and Specificity”[Mesh] OR sensitiv*[Title/Abstract] OR "sensitivity and specificity"[All Fields] OR “analytic validity”[all fields]	1119176
#22	Search “Diagnostic Errors”[Mesh] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic[MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp] OR “accuracy”[All Fields] OR "diagnosis"[MeSH] "diagnostic accuracy”[All Fields] OR “precision”[All Fields] OR "diagnostic error*"[All Fields]	87894
#23	Search “Predictive Value of Tests”[Mesh] OR "probability"[MeSH Terms] OR "probability"[All Fields] OR "likelihood"[All Fields] OR “false negative reactions”[MeSH] OR “false positive reactions”[MeSH] OR "predictive value of tests"[All Fields] OR "forecasting"[All Fields] OR "forecasting"[MeSH]	1129894
#24	Search #18 OR #19 OR #20 OR #21 OR #22 OR #23	2249689
#25	Search #10 AND (#16 OR #24)	2338
#26	Search #10 AND (#16 OR #24) Filters: Humans	2294
#27	Search #10 AND (#16 OR #24) Humans; English	2122
#28	Search #10 AND (#16 OR #24) Humans; English; Adult: 19+ years	1005
#29	Search #10 AND (#16 OR #24) Humans; English; Adult: 19+ years; Publication date from 1980/01/01	1005

Table A5. Embase search strategies 10-26-2012

Search	Queries	Number of Citations
Urinary Bladder Cancer Search		
#1	'bladder tumor'/exp AND ([embase]/lim OR [embase classic]/lim)	44,524
#2	urovysion AND ([embase]/lim OR [embase classic]/lim)	221
#3	ivdmia OR 'in vitro diagnostic multivariate index assay' AND ([embase]/lim OR [embase classic]/lim)	11
#4	#1 AND (#2 OR #3)	147
#5	'biological assay'/exp AND ([embase]/lim OR [embase classic]/lim)	27,952
#6	'predictive value of tests'/exp AND ([embase]/lim OR [embase classic]/lim)	20,862
#7	'proportional hazards models'/exp AND ([embase]/lim OR [embase classic]/lim)	24,303
#8	'treatment outcome'/exp AND ([embase]/lim OR [embase classic]/lim)	700,975
#9	'assay'/de OR assay OR assays OR test OR tests AND ([embase]/lim OR [embase classic]/lim)	2,963,585
#10	#5 OR #6 OR #7 OR #8 OR #9	3,557,123
#11	#4 AND #10	114
#12	'reproducibility of results'/exp OR 'reproducibility of results' AND ([embase]/lim OR [embase classic]/lim)	55,781
#13	'signal-to-noise ratio'/exp OR 'signal-to-noise ratio' AND ([embase]/lim OR [embase classic]/lim)	22,964
#14	'roc curve'/exp OR 'roc curve' OR 'receiver operating characteristic'/exp OR 'receiver operating characteristic' OR 'observer variation'/exp OR 'observer variation' AND ([embase]/lim OR [embase classic]/lim)	45,019
#15	'sensitivity and specificity'/exp OR 'sensitivity and specificity' OR 'sensitivity':ti OR 'sensitivity':ab OR 'analytic validity' AND ([embase]/lim OR [embase classic]/lim)	532,369
#16	'diagnostic errors'/exp OR 'diagnostic errors' OR 'diagnosis':ti OR 'diagnosis':ab OR 'diagnostic accuracy'/exp OR 'diagnostic accuracy' OR 'precision'/exp OR 'precision' AND ([embase]/lim OR [embase classic]/lim)	1,314,969
#17	'probability'/exp OR probability OR likelihood OR 'false negative reactions'/exp OR 'false negative reactions' OR 'false positive reactions'/exp OR 'false positive reactions' OR 'predictive value of tests'/exp OR 'predictive value of tests' OR 'forecasting'/exp OR forecasting AND ([embase]/lim OR [embase classic]/lim)	809,717
#18	#12 OR #13 OR #14 OR #15 OR #16 OR #17	2,381,955
#19	#4 AND (#10 OR #18)	142
#20	#19 AND ([adult]/lim OR [aged]/lim) AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim) AND [1980-2012]/py	32
Breast Cancer Search		
#1	'breast cancer'/exp AND ([embase]/lim OR [embase classic]/lim)	250,650
#2	'oncotype dx' OR '21 gene recurrence score' OR '21 gene recurrence' AND ([embase]/lim OR [embase classic]/lim)	404
#3	'mammaprint' OR '70 gene signature' AND ([embase]/lim OR [embase classic]/lim)	251
#4	ivdmia OR 'in vitro diagnostic multivariate index assay' AND ([embase]/lim OR [embase classic]/lim)	11
#5	#2 OR #3 OR #4	562
#6	#1 AND #5	520
#7	'biological assay'/exp AND ([embase]/lim OR [embase classic]/lim)	27,957
#8	'predictive value of tests'/exp AND ([embase]/lim OR [embase classic]/lim)	20,904
#9	'proportional hazards models'/exp AND ([embase]/lim OR [embase classic]/lim)	24,333
#10	'treatment outcome'/exp AND ([embase]/lim OR [embase classic]/lim)	701,175
#11	'assay' OR 'assay'/exp OR assay OR assays OR test OR tests AND ([embase]/lim OR [embase classic]/lim)	2,964,565
#12	#7 OR #8 OR #9 OR #10 OR #11	3,558,292
#13	#6 AND #12	386
#14	'reproducibility of results'/exp OR 'reproducibility of results' AND	55,807

Search	Queries	Number of Citations
	([embase]/lim OR [embase classic]/lim)	
#15	'signal-to-noise ratio'/exp OR 'signal-to-noise ratio' AND ([embase]/lim OR [embase classic]/lim)	22,980
#16	'roc curve'/exp OR 'roc curve' OR 'receiver operating characteristic'/exp OR 'receiver operating characteristic' OR 'observer variation'/exp OR 'observer variation' AND ([embase]/lim OR [embase classic]/lim)	45,053
#17	'sensitivity and specificity'/exp OR 'sensitivity and specificity' OR 'sensitivity':ti OR 'sensitivity':ab OR 'analytic validity' AND ([embase]/lim OR [embase classic]/lim)	532,590
#18	'diagnostic errors'/exp OR 'diagnostic errors' OR 'diagnosis':ti OR 'diagnosis':ab OR 'diagnostic accuracy'/exp OR 'diagnostic accuracy' OR 'precision'/exp OR 'precision' AND ([embase]/lim OR [embase classic]/lim)	1,315,423
#19	'probability' OR 'probability'/exp OR probability OR likelihood OR 'false negative reactions'/exp OR 'false negative reactions' OR 'false positive reactions'/exp OR 'false positive reactions' OR 'predictive value of tests'/exp OR 'predictive value of tests' OR 'forecasting' OR 'forecasting'/exp OR forecasting AND ([embase]/lim OR [embase classic]/lim)	810,061
#20	#14 OR #15 OR #16 OR #17 OR #18 OR #19	2,382,853
#21	#6 AND (#12 OR #20)	480
#22	#21 AND ([adult]/lim OR [aged]/lim) AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim) AND [1980-2012]/py	82
Colorectal Cancer Search		
#1	'colorectal cancer'/exp AND ([embase]/lim OR [embase classic]/lim)	64,587
#2	'microsatellite instability'/exp OR 'microsatellite instability' AND ([embase]/lim OR [embase classic]/lim)	7,045
#3	mlh1 AND ('promoter'/exp OR promoter) AND ('methylation'/exp OR methylation) AND ([embase]/lim OR [embase classic]/lim)	703
#4	kras AND ([embase]/lim OR [embase classic]/lim)	4,869
#5	braf AND ([embase]/lim OR [embase classic]/lim)	4,411
#6	'oncotype dx colon' OR '21 gene recurrence score' OR '21 gene recurrence' AND ([embase]/lim OR [embase classic]/lim)	86
#7	ivdmia OR 'in vitro diagnostic multivariate index assay' AND ([embase]/lim OR [embase classic]/lim)	11
#8	#2 OR #3 OR #4 OR #5 OR #6 OR #7	14,748
#9	#1 AND #8	4,149
#10	'biological assay'/exp AND ([embase]/lim OR [embase classic]/lim)	27,957
#11	'predictive value of tests'/exp AND ([embase]/lim OR [embase classic]/lim)	20,904
#12	'proportional hazards models'/exp AND ([embase]/lim OR [embase classic]/lim)	24,333
#13	'treatment outcome'/exp AND ([embase]/lim OR [embase classic]/lim)	701,175
#14	'assay' OR 'assay'/exp OR assay OR assays OR test OR tests AND ([embase]/lim OR [embase classic]/lim)	2,964,565
#15	#10 OR #11 OR #12 OR #13 OR #14	3,558,292
#16	#9 AND #15	1,190
#17	'reproducibility of results'/exp OR 'reproducibility of results' AND ([embase]/lim OR [embase classic]/lim)	55,807
#18	'signal-to-noise ratio'/exp OR 'signal-to-noise ratio' AND ([embase]/lim OR [embase classic]/lim)	22,980
#19	'roc curve'/exp OR 'roc curve' OR 'receiver operating characteristic'/exp OR 'receiver operating characteristic' OR 'observer variation'/exp OR 'observer variation' AND ([embase]/lim OR [embase classic]/lim)	45,053
#20	'sensitivity and specificity'/exp OR 'sensitivity and specificity' OR 'sensitivity':ti OR 'sensitivity':ab OR 'analytic validity' AND ([embase]/lim OR [embase classic]/lim)	532,590
#21	'diagnostic errors'/exp OR 'diagnostic errors' OR 'diagnosis':ti OR 'diagnosis':ab OR 'diagnostic accuracy'/exp OR 'diagnostic accuracy' OR 'precision'/exp OR 'precision' AND ([embase]/lim OR [embase	1,315,423

Search	Queries	Number of Citations
	classic]/lim)	
#22	'probability' OR 'probability'/exp OR probability OR likelihood OR 'false negative reactions'/exp OR 'false negative reactions' OR 'false positive reactions'/exp OR 'false positive reactions' OR 'predictive value of tests'/exp OR 'predictive value of tests' OR 'forecasting' OR 'forecasting'/exp OR forecasting AND ([embase]/lim OR [embase classic]/lim)	810,061
#23	#17 OR #18 OR #19 OR #20 OR #21 OR #22	2,382,853
#24	#9 AND (#15 OR #23)	2,184
#25	#24 AND ([adult]/lim OR [aged]/lim) AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim) AND [1980-2012]/py	605
Lung Cancer Search		
#1	'lung cancer'/exp AND ([embase]/lim OR [embase classic]/lim)	176,206
#2	'lung carcinoma'/exp AND ([embase]/lim OR [embase classic]/lim)	90,226
#3	#1 OR #2	176,206
#4	'eml4-alk' AND ([embase]/lim OR [embase classic]/lim)	337
#5	alk AND ([embase]/lim OR [embase classic]/lim)	4,992
#6	egfr AND ([embase]/lim OR [embase classic]/lim)	30,017
#7	kras AND ([embase]/lim OR [embase classic]/lim)	4,869
#8	ivdmia OR 'in vitro diagnostic multivariate index assay' AND ([embase]/lim OR [embase classic]/lim)	11
#9	#4 OR #5 OR #6 OR #7 OR #8	37,784
#10	#3 AND #9	6,492
#11	'biological assay'/exp AND ([embase]/lim OR [embase classic]/lim)	27,957
#12	'predictive value of tests'/exp AND ([embase]/lim OR [embase classic]/lim)	20,904
#13	'proportional hazards models'/exp AND ([embase]/lim OR [embase classic]/lim)	24,333
#14	'treatment outcome'/exp AND ([embase]/lim OR [embase classic]/lim)	701,175
#15	'assay' OR 'assay'/exp OR assay OR assays OR test OR tests AND ([embase]/lim OR [embase classic]/lim)	2,964,565
#16	#11 OR #12 OR #13 OR #14 OR #15	3,558,292
#17	#10 AND #16	2,150
#18	'reproducibility of results'/exp OR 'reproducibility of results' AND ([embase]/lim OR [embase classic]/lim)	55,807
#19	'signal-to-noise ratio'/exp OR 'signal-to-noise ratio' AND ([embase]/lim OR [embase classic]/lim)	22,980
#20	'roc curve'/exp OR 'roc curve' OR 'receiver operating characteristic'/exp OR 'receiver operating characteristic' OR 'observer variation'/exp OR 'observer variation' AND ([embase]/lim OR [embase classic]/lim)	45,053
#21	'sensitivity and specificity'/exp OR 'sensitivity and specificity' OR 'sensitivity':ti OR 'sensitivity':ab OR 'analytic validity' AND ([embase]/lim OR [embase classic]/lim)	532,590
#22	'diagnostic errors'/exp OR 'diagnostic errors' OR 'diagnosis':ti OR 'diagnosis':ab OR 'diagnostic accuracy'/exp OR 'diagnostic accuracy' OR 'precision'/exp OR 'precision' AND ([embase]/lim OR [embase classic]/lim)	1,315,423
#23	'probability' OR 'probability'/exp OR probability OR likelihood OR 'false negative reactions'/exp OR 'false negative reactions' OR 'false positive reactions'/exp OR 'false positive reactions' OR 'predictive value of tests'/exp OR 'predictive value of tests' OR 'forecasting' OR 'forecasting'/exp OR forecasting AND ([embase]/lim OR [embase classic]/lim)	810,061
#24	#18 OR #19 OR #20 OR #21 OR #22 OR #23	2,382,853
#25	#10 AND (#16 OR #24)	3,437
#26	#25 AND ([adult]/lim OR [aged]/lim) AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim) AND [1980-2012]/py	878

Table A6. Cochrane search strategies 10-29-2012

Search	Queries	Number of Citations
Urinary Bladder Cancer Search		
#1	MeSH descriptor: [Urinary Bladder Neoplasms] explode all trees	919
#2	urovysion	2
#3	ivdmia	1
#4	"in vitro multivariate index assay"	0
#5	#1 and (#2 or #3 or #4)	2
#6	MeSH descriptor: [Biological Assay] explode all trees	152
#7	MeSH descriptor: [Predictive Value of Tests] explode all trees	5083
#8	MeSH descriptor: [Proportional Hazards Models] explode all trees	2827
#9	MeSH descriptor: [Outcome and Process Assessment (Health Care)] explode all trees	83811
#10	assay	11447
#11	assays	11447
#12	test	144378
#13	tests	144378
#14	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13	215226
#15	MeSH descriptor: [Reproducibility of Results] explode all trees	8077
#16	"reproducibility of results"	8375
#17	MeSH descriptor: [Signal-To-Noise Ratio] explode all trees	0
#18	"signal-to-noise ratio"	145
#19	MeSH descriptor: [ROC Curve] explode all trees	851
#20	"ROC Curve"	1113
#21	"receiver operating characteristic"	1107
#22	MeSH descriptor: [Observer Variation] explode all trees	1556
#23	“observer variation”	2444
#24	MeSH descriptor: [Sensitivity and Specificity] explode all trees	13656
#25	sensitivity:ti (Word variations have been searched)	2714
#26	sensitivity:ab (Word variations have been searched)	15456
#27	"sensitivity and specificity"	11058
#28	“analytic validity”	1481
#29	MeSH descriptor: [Diagnostic Errors] explode all trees	2362
#30	diagnos*:ti,ab	34133
#31	MeSH descriptor: [Diagnosis] this term only	79
#32	MeSH descriptor: [Diagnosis, Differential] this term only	1338
#33	Any MeSH descriptor with qualifier(s): [Diagnosis - DI]	33493
#34	accuracy	9811
#35	MeSH descriptor: [Diagnosis] explode all trees	221504
#36	diagnostic accuracy	4126
#37	precision	2746
#38	"diagnostic error*"	288
#39	MeSH descriptor: [Predictive Value of Tests] explode all trees	5083
#40	MeSH descriptor: [Probability] explode all trees	31596
#41	probability	11646
#42	likelihood	6058
#43	MeSH descriptor: [False Negative Reactions] explode all trees	314
#44	MeSH descriptor: [False Positive Reactions] explode all trees	470
#45	"predictive value of test*"	5202
#46	forecasting	588
#47	MeSH descriptor: [Forecasting] explode all trees	423
#48	#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47	275562
#49	#5 and (#14 or #48)	2
#50	#5 and (#14 or #48) from 1980	2
Breast Cancer Search		

Search	Queries	Number of Citations
#1	MeSH descriptor: [Breast Neoplasms] explode all trees	7522
#2	"oncotype DX"	10
#3	"21 gene recurrence score"	6
#4	"21 gene recurrence"	6
#5	Mammaprint	8
#6	"70 gene signature"	3
#7	ivdmia	1
#8	"in vitro multivariate index assay"	0
#9	#1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)	21
#10	MeSH descriptor: [Biological Assay] explode all trees	152
#11	MeSH descriptor: [Predictive Value of Tests] explode all trees	5083
#12	MeSH descriptor: [Proportional Hazards Models] explode all trees	2827
#13	MeSH descriptor: [Outcome and Process Assessment (Health Care)] explode all trees	83811
#14	assay	11447
#15	assays	11447
#16	test	144378
#17	tests	144378
#18	#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17	215226
#19	MeSH descriptor: [Reproducibility of Results] explode all trees	8077
#20	"reproducibility of results"	8375
#21	MeSH descriptor: [Signal-To-Noise Ratio] explode all trees	0
#22	"signal-to-noise ratio"	145
#23	MeSH descriptor: [ROC Curve] explode all trees	851
#24	"ROC Curve"	1113
#25	"receiver operating characteristic"	1107
#26	MeSH descriptor: [Observer Variation] explode all trees	1556
#27	“observer variation”	2444
#28	MeSH descriptor: [Sensitivity and Specificity] explode all trees	13656
#29	sensitivity:ti (Word variations have been searched)	2714
#30	sensitivity:ab (Word variations have been searched)	15456
#31	"sensitivity and specificity"	11058
#32	“analytic validity”	1481
#33	MeSH descriptor: [Diagnostic Errors] explode all trees	2362
#34	diagnos*:ti,ab	34133
#35	MeSH descriptor: [Diagnosis] this term only	79
#36	MeSH descriptor: [Diagnosis, Differential] this term only	1338
#37	Any MeSH descriptor with qualifier(s): [Diagnosis - DI]	33493
#38	accuracy	9811
#39	MeSH descriptor: [Diagnosis] explode all trees	221504
#40	diagnostic accuracy	4126
#41	precision	2746
#42	"diagnostic error*"	288
#43	MeSH descriptor: [Predictive Value of Tests] explode all trees	5083
#44	MeSH descriptor: [Probability] explode all trees	31596
#45	probability	11646
#46	likelihood	6058
#47	MeSH descriptor: [False Negative Reactions] explode all trees	314
#48	MeSH descriptor: [False Positive Reactions] explode all trees	470
#49	"predictive value of test*"	5202
#50	forecasting	588
#51	MeSH descriptor: [Forecasting] explode all trees	423
#52	#19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51	275562
#53	#9 and (#18 or #52)	20

Search	Queries	Number of Citations
#54	#9 and (#18 or #52) from 1980	20
Colorectal Cancer Search		
#1	MeSH descriptor: [Colorectal Neoplasms] explode all trees	4390
#2	MeSH descriptor: [Microsatellite Instability] explode all trees	21
#3	"Microsatellite Instability"	54
#4	MLH1 promoter methylation	2
#5	KRAS protein, human	58
#6	KRAS	93
#7	BRAF protein, human	27
#8	"Oncotype DX Colon"	0
#9	"21 gene recurrence score"	6
#10	"21 gene recurrence"	6
#11	ivdmia	1
#12	"in vitro multivariate index assay"	0
#13	#1 and (#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12)	87
#14	MeSH descriptor: [Biological Assay] explode all trees	152
#15	MeSH descriptor: [Predictive Value of Tests] explode all trees	5083
#16	MeSH descriptor: [Proportional Hazards Models] explode all trees	2827
#17	MeSH descriptor: [Outcome and Process Assessment (Health Care)] explode all trees	83811
#18	assay	11447
#19	assays	11447
#20	test	144378
#21	tests	144378
#22	#14 or #15 or #16 or #17 or #18 or #19 or #20 or #21	215226
#23	MeSH descriptor: [Reproducibility of Results] explode all trees	8077
#24	"reproducibility of results"	8375
#25	MeSH descriptor: [Signal-To-Noise Ratio] explode all trees	0
#26	"signal-to-noise ratio"	145
#27	MeSH descriptor: [ROC Curve] explode all trees	851
#28	"ROC Curve"	1113
#29	"receiver operating characteristic"	1107
#30	MeSH descriptor: [Observer Variation] explode all trees	1556
#31	“observer variation”	2444
#32	MeSH descriptor: [Sensitivity and Specificity] explode all trees	13656
#33	sensitivity:ti (Word variations have been searched)	2714
#34	sensitivity:ab (Word variations have been searched)	15456
#35	"sensitivity and specificity"	11058
#36	“analytic validity”	1481
#37	MeSH descriptor: [Diagnostic Errors] explode all trees	2362
#38	diagnos*:ti,ab	34133
#39	MeSH descriptor: [Diagnosis] this term only	79
#40	MeSH descriptor: [Diagnosis, Differential] this term only	1338
#41	Any MeSH descriptor with qualifier(s): [Diagnosis - DI]	33493
#42	accuracy	9811
#43	MeSH descriptor: [Diagnosis] explode all trees	221504
#44	diagnostic accuracy	4126
#45	precision	2746
#46	"diagnostic error*"	288
#47	MeSH descriptor: [Predictive Value of Tests] explode all trees	5083
#48	MeSH descriptor: [Probability] explode all trees	31596
#49	probability	11646
#50	likelihood	6058
#51	MeSH descriptor: [False Negative Reactions] explode all trees	314
#52	MeSH descriptor: [False Positive Reactions] explode all trees	470
#53	"predictive value of test*"	5202
#54	forecasting	588

Search	Queries	Number of Citations
#55	MeSH descriptor: [Forecasting] explode all trees	423
#56	#23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55	275562
#57	#13 and (#22 or #56)	71
#58	#13 and (#22 or #56) from 1980	71
Lung Cancer Search		
#1	MeSH descriptor: [Lung Neoplasms] explode all trees	4189
#2	MeSH descriptor: [Carcinoma, Bronchogenic] explode all trees	2159
#3	#1 or #2	4189
#4	EML4-ALK fusion protein, human	0
#5	ALK	115
#6	EGFR protein, human	177
#7	EGFR	526
#8	KRAS protein, human	58
#9	KRAS	93
#10	ivdmia	1
#11	"in vitro multivariate index assay"	0
#12	#3 and (#4 or #5 or #6 or #8 or #9 or #10 or #11)	56
#13	MeSH descriptor: [Biological Assay] explode all trees	152
#14	MeSH descriptor: [Predictive Value of Tests] explode all trees	5083
#15	MeSH descriptor: [Proportional Hazards Models] explode all trees	2827
#16	MeSH descriptor: [Outcome and Process Assessment (Health Care)] explode all trees	83811
#17	assay	11447
#18	assays	11447
#19	test	144378
#20	tests	144378
#21	#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20	215226
#22	MeSH descriptor: [Reproducibility of Results] explode all trees	8077
#23	"reproducibility of results"	8375
#24	MeSH descriptor: [Signal-To-Noise Ratio] explode all trees	0
#25	"signal-to-noise ratio"	145
#26	MeSH descriptor: [ROC Curve] explode all trees	851
#27	"ROC Curve"	1113
#28	"receiver operating characteristic"	1107
#29	MeSH descriptor: [Observer Variation] explode all trees	1556
#30	“observer variation”	2444
#31	MeSH descriptor: [Sensitivity and Specificity] explode all trees	13656
#32	sensitivity:ti (Word variations have been searched)	2714
#33	sensitivity:ab (Word variations have been searched)	15456
#34	"sensitivity and specificity"	11058
#35	“analytic validity”	1481
#36	MeSH descriptor: [Diagnostic Errors] explode all trees	2362
#37	diagnos*:ti,ab	34133
#38	MeSH descriptor: [Diagnosis] this term only	79
#39	MeSH descriptor: [Diagnosis, Differential] this term only	1338
#40	Any MeSH descriptor with qualifier(s): [Diagnosis - DI]	33493
#41	accuracy	9811
#42	MeSH descriptor: [Diagnosis] explode all trees	221504
#43	diagnostic accuracy	4126
#44	precision	2746
#45	"diagnostic error*"	288
#46	MeSH descriptor: [Predictive Value of Tests] explode all trees	5083
#47	MeSH descriptor: [Probability] explode all trees	31596
#48	probability	11646

Search	Queries	Number of Citations
#49	likelihood	6058
#50	MeSH descriptor: [False Negative Reactions] explode all trees	314
#51	MeSH descriptor: [False Positive Reactions] explode all trees	470
#52	"predictive value of test*"	5202
#53	forecasting	588
#54	MeSH descriptor: [Forecasting] explode all trees	423
#55	#22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54	275562
#56	#12 and (#21 or #55)	44
#57	#12 and (#21 or #55) from 1980	44

Appendix B. Exclusions

Exclusion Code Key:

- EXC1: Systematic Review
- EXC2: Wrong publication type
- EXC3: Wrong population
- EXC4: Wrong intervention
- EXC5: Wrong or no comparator
- EXC6: Wrong or no outcome
- EXC7: Wrong study design
- EXC8: Does not apply to a key question
- EXC9: Irretrievable

1. Bladder cancer surveillance (Structured abstract). Health Technology Assessment Database. 2007(3)PMID: HTA-32010001141. EXC1
2. Epidermal growth factor receptor mutations and tyrosine kinase inhibitor therapy in advanced non-small-cell lung cancer (Structured abstract). Health Technology Assessment Database. 2007(3)PMID: HTA-32010000201. EXC2
3. CYP2D6 pharmacogenomics of tamoxifen treatment (Structured abstract). Health Technology Assessment Database. 2008(3)PMID: HTA-32010000213. EXC2
4. Oncotype DX prognostic and predictive test for early breast cancer (Structured abstract). Health Technology Assessment Database. 2008(3)PMID: HTA-32010000622. EXC2
5. KRAS mutations and epidermal growth factor receptor inhibitor therapy in metastatic colorectal cancer (Structured abstract). Health Technology Assessment Database. 2008(3)PMID: HTA-32010000218. EXC2
6. MammaPrint (gene test) for breast cancer - prognostic test: horizon scanning technology briefing (Project record). Health Technology Assessment Database. 2009(3)PMID: HTA-32008100372. EXC2
7. Gene expression profiling in women with lymph-node-positive breast cancer to select adjuvant chemotherapy treatment (Structured abstract). Health Technology Assessment Database. 2010(3)PMID: HTA-32011000017. EXC2
8. KRAS testing for anti-EGFR therapy in advanced colorectal cancer: an evidence-based and economic analysis (Provisional abstract). Database of Abstracts of Reviews of Effects. 2010(3):1. PMID: DARE-12011004254. EXC2
9. Epidermal growth factor receptor mutation (EGFR) testing for prediction of response to EGFR-targeting tyrosine kinase inhibitor (TKI) drugs in patients with advanced non-small-cell lung cancer: an evidence-based analysis (Provisional abstract). Database of Abstracts of Reviews of Effects. 2010(3):1. PMID: DARE-12011004253. EXC1
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Appendix C. Criteria for Evaluating Risk of Bias

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3396	Abbot	2011

ROB RATING: UNCLEAR

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low	*	Medium	*	High	*	N/A	
Risk of bias for KQ 3:	Low		Medium		High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (__)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1. What is the study design?						
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
2. For RCTs, were randomization and allocation concealment adequate?						
3. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?						
4. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?						
5. Were groups similar at baseline?						
6. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?						
7. Were outcomes assessed using valid and reliable measures, implemented consistently						

across all study participants?							
8. Was overall attrition less than 30%?							
9. Was differential attrition less than 15%?							
10. Does the analysis control for baseline differences between groups?							
11. Does the analysis account for differences in treatment received by the groups?							
12. Are the statistical methods used to assess the outcomes appropriate?							
13. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?							
Comments:							

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (___)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?			X				
Was a case-control design avoided?	X						
Did the study avoid inappropriate exclusions?			X				
Could the selection of patients have introduced bias?							X
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?	X						
If a threshold was used, was it pre-specified?			X				
Could the conduct or interpretation of the index test have introduced bias?							X
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?				X			
Were the reference standard results interpreted without knowledge of the results of the index test?				X			
Could the reference standard, its conduct, or its interpretation have introduced bias?							X
Domain 4: Flow and Timing							
Did all patients receive a reference standard?				X			
Did patients receive the same reference standard?				X			
Were all patients included in the analysis?				X			
Could the patient flow have introduced bias?							X
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
159	Ademuyiwa	2011

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium		High		N/A	
Risk of bias for KQ 4a:	Low		Medium	x	High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
14. What is the study design?				**x**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
15. For RCTs, were randomization and allocation concealment adequate?					x	
16. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	x					
17. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	x					
18. Were groups similar at baseline?					x	
19. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?	x					
20. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?		x				
21. Was overall attrition less than 30%?					x	
22. Was differential attrition less than 15%?					x	
23. Does the analysis control for baseline	x					

differences between groups?						
24. Does the analysis account for differences in treatment received by the groups?					x	
25. Are the statistical methods used to assess the outcomes appropriate?	x					
26. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	x					
Comments: This analysis claims that the Oncotype test changes decision making based on the study of hypotherical treatment decisions made by only TWO medical oncologists who disagreed in 20% of the case on what their treatment recommendation would be, in which case the authors just threw out one opinion. The design of the study is fine, but the conclusions they drew from it are vastly over-inflated.						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (X__)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
153	Albanell	2011

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium		High		N/A	
Risk of bias for KQ 4a:	Low	X	Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
27. What is the study design?			**x**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
28. For RCTs, were randomization and allocation concealment adequate?					x	
29. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	x					
30. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	x					pre/post test design
31. Were groups similar at baseline?					x	
32. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?	x					in pretest yes
33. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	x					
34. Was overall attrition less than 30%?				x		
35. Was differential attrition less than 15%?				x		
36. Does the analysis control for baseline	x					

differences between groups?						
37. Does the analysis account for differences in treatment received by the groups?	x					
38. Are the statistical methods used to assess the outcomes appropriate?	x					
39. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?						
Comments: I marked this as a prospective cohort rather than a case series (as in other similar pre/post test decision making studies) b/c patients were enrolled prospectively for this purpose rather than their cases being used as examples retrospectively for a group of physicians.						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
2772	An	2012

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium	x	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
40. What is the study design?				**x**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
41. For RCTs, were randomization and allocation concealment adequate?					x	
42. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	x					
43. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	x					
44. Were groups similar at baseline?				x		
45. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?		x				
46. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	x					
47. Was overall attrition less than 30%?					x	
48. Was differential attrition less than 15%?					x	
49. Does the analysis control for baseline	x					

differences between groups?						
50. Does the analysis account for differences in treatment received by the groups?		x				
51. Are the statistical methods used to assess the outcomes appropriate?	x					
52. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	x					
Comments: adjusted HRs for survival by EGFR status are reported ONLY for stage I patients, text reports that EGFR was not a significant predictor in the overall sample. Hard to know how to interpret.						

Key Question 2					If study does NOT apply to this KQ, place an 'X' here (_X_)		
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
2774	Angulo	2012

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low	x	Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium		High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (_X_)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
53. What is the study design?						
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
54. For RCTs, were randomization and allocation concealment adequate?						
55. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?						
56. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?						
57. Were groups similar at baseline?						
58. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?						
59. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?						
60. Was overall attrition less than 30%?						
61. Was differential attrition less than 15%?						
62. Does the analysis control for baseline						

differences between groups?							
63. Does the analysis account for differences in treatment received by the groups?							
64. Are the statistical methods used to assess the outcomes appropriate?							
65. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?							
Comments:							

Key Question 2					If study does NOT apply to this KQ, place an 'X' here (___)		
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?			x				
Was a case-control design avoided?	x						
Did the study avoid inappropriate exclusions?			x				
Could the selection of patients have introduced bias?							x
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?			x				
If a threshold was used, was it pre-specified?	x						
Could the conduct or interpretation of the index test have introduced bias?					x		
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?	x						
Were the reference standard results interpreted without knowledge of the results of the index test?	x						
Could the reference standard, its conduct, or its interpretation have introduced bias?					x		
Domain 4: Flow and Timing							
Did all patients receive a reference standard?	x						
Did patients receive the same reference standard?	x						
Were all patients included in the analysis?		x					
Could the patient flow have introduced bias?					x		
Comments: 3 of 136 pts not included due to insufficient DNA material. How patient tissues were selected from those available at the institution (consecutive, random, other) was not reported.							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3435	Bando	2012

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium	X	High		N/A	
Risk of bias for KQ 3:	Low		Medium		High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (__)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
66. What is the study design?						
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
67. For RCTs, were randomization and allocation concealment adequate?						
68. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?						
69. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?						
70. Were groups similar at baseline?						
71. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?						
72. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?						
73. Was overall attrition less than 30%?						

74. Was differential attrition less than 15%?						
75. Does the analysis control for baseline differences between groups?						
76. Does the analysis account for differences in treatment received by the groups?						
77. Are the statistical methods used to assess the outcomes appropriate?						
78. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?						
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (___)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?	X						
Was a case-control design avoided?	X						
Did the study avoid inappropriate exclusions?			X				
Could the selection of patients have introduced bias?					X		
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?	X						
If a threshold was used, was it pre-specified?			X				
Could the conduct or interpretation of the index test have introduced bias?					X		
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?	X						
Were the reference standard results interpreted without knowledge of the results of the index test?	X						
Could the reference standard, its conduct, or its interpretation have introduced bias?					X		
Domain 4: Flow and Timing							
Did all patients receive a reference standard?	X						
Did patients receive the same reference standard?	X						
Were all patients included in the analysis?	X						
Could the patient flow have introduced bias?					X		
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
4021	Bargallo	2012

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium		High		N/A	X
Risk of bias for KQ 4a:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
79. What is the study design?			**X**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
80. For RCTs, were randomization and allocation concealment adequate?					X	
81. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					Consecutive sample
82. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
83. Were groups similar at baseline?				X		
84. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		But, not as important as some studies since the outcome is the questionnaire result
85. Were outcomes assessed using valid and reliable measures, implemented consistently				X		Multidisciplinary team completed

across all study participants?						questionnaires; no other information provided to determine validity and reliability of measures
86. Was overall attrition less than 30%?	X					
87. Was differential attrition less than 15%?	X					
88. Does the analysis control for baseline differences between groups?		X				
89. Does the analysis account for differences in treatment received by the groups?					X	
90. Are the statistical methods used to assess the outcomes appropriate?	X					
91. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?					X	
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
272	Bazan	2005

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium	x	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
92. What is the study design?			**x**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
93. For RCTs, were randomization and allocation concealment adequate?					x	
94. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	x					
95. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	x					
96. Were groups similar at baseline?				x		
97. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				x		Outcome is survival, so blinding unlikely to matter
98. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	x					Medical records
99. Was overall attrition less than 30%?				x		
100. Was differential attrition less than 15%?				x		

101. Does the analysis control for baseline differences between groups?	x					
102. Does the analysis account for differences in treatment received by the groups?			x			Adjusts for surgery but not receipt of chemo
103. Are the statistical methods used to assess the outcomes appropriate?	x					
104. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	x					
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_x_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
1813	Beau-Faller	2011

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low	X	Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium		High		N/A	X
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (_X_)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
105. What is the study design?						
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
106. For RCTs, were randomization and allocation concealment adequate?						
107. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?						
108. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?						
109. Were groups similar at baseline?						
110. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?						
111. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?						
112. Was overall attrition less than 30%?						
113. Was differential attrition less than 15%?						
114. Does the analysis control for baseline						

differences between groups?							
115. Does the analysis account for differences in treatment received by the groups?							
116. Are the statistical methods used to assess the outcomes appropriate?							
117. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?							
Comments:							

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (___)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?			X				
Was a case-control design avoided?	X						
Did the study avoid inappropriate exclusions?	X						
Could the selection of patients have introduced bias?					X		
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?	X						
If a threshold was used, was it pre-specified?	X						
Could the conduct or interpretation of the index test have introduced bias?					X		
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?	X						
Were the reference standard results interpreted without knowledge of the results of the index test?	X						
Could the reference standard, its conduct, or its interpretation have introduced bias?					X		
Domain 4: Flow and Timing							
Did all patients receive a reference standard?	X						
Did patients receive the same reference standard?	X						
Were all patients included in the analysis?		X					
Could the patient flow have introduced bias?					X		
Comments: 6 frozen samples (out of 74) were excluded from portions of the analyses because they contained less than 30% tumor cells							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
1814	Beau-Faller	2009

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low	X	Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium		High		N/A	X
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (_X_)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
118. What is the study design?						
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
119. For RCTs, were randomization and allocation concealment adequate?						
120. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?						
121. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?						
122. Were groups similar at baseline?						
123. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?						
124. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?						
125. Was overall attrition less than 30%?						
126. Was differential attrition less than 15%?						
127. Does the analysis control for baseline						

differences between groups?							
128. Does the analysis account for differences in treatment received by the groups?							
129. Are the statistical methods used to assess the outcomes appropriate?							
130. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?							
Comments:							

Key Question 2					If study does NOT apply to this KQ, place an 'X' here (___)		
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?	X						
Was a case-control design avoided?	X						
Did the study avoid inappropriate exclusions?	X						
Could the selection of patients have introduced bias?					X		
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?			X				
If a threshold was used, was it pre-specified?	X						
Could the conduct or interpretation of the index test have introduced bias?					X		
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?	X						
Were the reference standard results interpreted without knowledge of the results of the index test?	X						
Could the reference standard, its conduct, or its interpretation have introduced bias?					X		
Domain 4: Flow and Timing							
Did all patients receive a reference standard?	X						
Did patients receive the same reference standard?	X						
Were all patients included in the analysis?	X						
Could the patient flow have introduced bias?					X		
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
4027	Brenner	2013

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium		High		N/A	X
Risk of bias for KQ 4a:	Low		Medium		High	X	N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
131. What is the study design?			**X**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
132. For RCTs, were randomization and allocation concealment adequate?					X	
133. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?				X		Unclear, but seems to imply all patients during the time frame listed
134. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
135. Were groups similar at baseline?				X		
136. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		They don't report blinding of outcome assessors.
137. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		No description of how they

						were ascertained
138. Was overall attrition less than 30%?	X					
139. Was differential attrition less than 15%?	X					
140. Does the analysis control for baseline differences between groups?					X	
141. Does the analysis account for differences in treatment received by the groups?					X	
142. Are the statistical methods used to assess the outcomes appropriate?	X					
143. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?					X	
Comments: Very limited reporting of study design and methods. At least medium risk of ascertainment/measurement bias. There are multiple reasons why someone might receive a different treatment than initially recommended (e.g., patient preferences, other medical problems limiting ability to undergo treatment). This study assumes that the test result is the reason, without attempting to measure causality accurately. They did not assess treatment recommendation before vs. after; they assessed treatment recommendation before vs. what ultimately happened.						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
165	Bueno-de-Mesquita	2007

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium		High		N/A	X
Risk of bias for KQ 4a:	Low	X	Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
144. What is the study design?			**X**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
145. For RCTs, were randomization and allocation concealment adequate?					X	
146. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
147. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
148. Were groups similar at baseline?		X				
149. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		Pathologists were masked, but the outcomes of relevance for this article were decisions about treatment (NR if the

						investigators handling that data were masked to MammaPrint results)
150. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	X					
151. Was overall attrition less than 30%?	X					
152. Was differential attrition less than 15%?	X					
153. Does the analysis control for baseline differences between groups?		X				But, not essential to do so for the question of whether having the MammaPrint information changes decisions
154. Does the analysis account for differences in treatment received by the groups?		X				But, not essential for this question
155. Are the statistical methods used to assess the outcomes appropriate?	X					
156. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?					X	
Comments: Low risk of bias for assessing whether treatment decisions differ when using only the Dutch CBO guidelines (clinical information) and when also using MammaPrint results. Related to applicability of this study, the Dutch guidelines only include age, grade, and size, so whether adding MammaPrint result to decisions based on these 3 things doesn't quite get us the information of relevance to current practice in the US. We would need decisions based on all the current known prognostic factors, and then to determine whether they change with adding MammaPrint. In Table 2, they report a similar rate of discordance between Adjuvant! Online and MammaPrint as they report for the Dutch CBO guidelines and MammaPrint. This might suggest that adding MammaPrint to Adjuvant! Online would change a similar proportion of decisions as when adding it to the Dutch guidelines.						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have							

introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3363	Bueno de Mesquita	2009

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low	X	Medium		High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
157. What is the study design?			**X**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
158. For RCTs, were randomization and allocation concealment adequate?					X	
159. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
160. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
161. Were groups similar at baseline?				X		
162. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
163. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	X					
164. Was overall attrition less than 30%?	X					
165. Was differential attrition less than 15%?	X					
166. Does the analysis control for baseline		X				

differences between groups?						
167. Does the analysis account for differences in treatment received by the groups?		X				
168. Are the statistical methods used to assess the outcomes appropriate?	X					
169. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments:						

Key Question 2					If study does NOT apply to this KQ, place an 'X' here (___)		
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
166	Buyse	2006

RATING: UNCLEAR

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium		High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:	unclear							

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (__)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
170. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
171. For RCTs, were randomization and allocation concealment adequate?					X	
172. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
173. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
174. Were groups similar at baseline?		X				
175. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
176. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	X					
177. Was overall attrition less than 30%?				X		

178. Was differential attrition less than 15%?				X		
179. Does the analysis control for baseline differences between groups?				X		
180. Does the analysis account for differences in treatment received by the groups?		X				
181. Are the statistical methods used to assess the outcomes appropriate?	X					
182. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (___)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments: Reference standard here was pyrosequencing							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3405	Cartwright	Unknown

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium		High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High	X	N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:	.Cross sectional survey of oncologists who had previously ordered oncotype DX							

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (__)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	non-RCT	Prospective cohort study	Retrospective cohort study	Case-control study	Case Series
183. What is the study design?		**THIS STUDY WAS A CROSS SECTIONAL SURVEY OF ONCOLOGISTS SO DOES NOT FIT ANY OF THESE**				
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
184. For RCTs, were randomization and allocation concealment adequate?					X	
185. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?				X		

186. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?					X	
187. Were groups similar at baseline?					X	
188. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
189. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		
190. Was overall attrition less than 30%?			X			
191. Was differential attrition less than 15%?					X	
192. Does the analysis control for baseline differences between groups?					X	
193. Does the analysis account for differences in treatment received by the groups?					X	
194. Are the statistical methods used to assess the outcomes appropriate?	X					
195. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?						
Comments: Abstract shows only preliminary analysis and says full data will be presented at meeting.						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (___)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
385	Chang	2006

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	x
Risk of bias for KQ 2:	Low		Medium		High		N/A	x
Risk of bias for KQ 3:	Low		Medium	x	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	x
Risk of bias for KQ 4b:	Low		Medium		High		N/A	x
Risk of bias for KQ 5:	Low		Medium		High		N/A	x
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
196. What is the study design?			**x**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
197. For RCTs, were randomization and allocation concealment adequate?					x	
198. xDid the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	x					
199. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	x					
200. Were groups similar at baseline?		x				
201. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?	x					
202. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	x					
203. Was overall attrition less than 30%?	x					
204. Was differential attrition less than 15%?	x					
205. Does the analysis control for baseline		x				BRAF

differences between groups?						differences
206. Does the analysis account for differences in treatment received by the groups?		X				
207. Are the statistical methods used to assess the outcomes appropriate?	X					
208. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments: Treatment not controlled for despite it being a prospective study.						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (___)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3350	Clark-Langone	2010

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium	X	High		N/A	
Risk of bias for KQ 3:	Low		Medium		High		N/A	X
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (_X_)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
209. What is the study design?						
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
210. For RCTs, were randomization and allocation concealment adequate?						
211. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?						
212. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?						
213. Were groups similar at baseline?						
214. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?						
215. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?						
216. Was overall attrition less than 30%?						
217. Was differential attrition less than 15%?						
218. Does the analysis control for baseline						

differences between groups?						
219. Does the analysis account for differences in treatment received by the groups?						
220. Are the statistical methods used to assess the outcomes appropriate?						
221. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?						
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (___)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?			X				
Was a case-control design avoided?	X						
Did the study avoid inappropriate exclusions?	X						
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?				X			
If a threshold was used, was it pre-specified?				X			
Could the conduct or interpretation of the index test have introduced bias?					X		
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?					X		
Domain 4: Flow and Timing							
Did all patients receive a reference standard?				X			
Did patients receive the same reference standard?				X			
Were all patients included in the analysis?				X			
Could the patient flow have introduced bias?					X		
Comments:This is a paper that is looking at LOD, reproducibility, cross lab comparisons etc. Many of these criteria are in applicable							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
4000	Cronin	2007

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High				N/A	X
Risk of bias for KQ 2:	Low		Medium		High		Unclear	X	N/A	
Risk of bias for KQ 3:	Low		Medium		High				N/A	X
Risk of bias for KQ 4a:	Low		Medium		High				N/A	X
Risk of bias for KQ 4b:	Low		Medium		High				N/A	X
Risk of bias for KQ 5:	Low		Medium		High				N/A	X
Explain any **High** ratings:										

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (_X_)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
222. What is the study design?						
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
223. For RCTs, were randomization and allocation concealment adequate?						
224. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?						
225. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?						
226. Were groups similar at baseline?						
227. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?						
228. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?						
229. Was overall attrition less than 30%?						
230. Was differential attrition less than 15%?						
231. Does the analysis control for baseline						

differences between groups?							
232. Does the analysis account for differences in treatment received by the groups?							
233. Are the statistical methods used to assess the outcomes appropriate?							
234. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?							
Comments:							

Key Question 2					If study does NOT apply to this KQ, place an 'X' here (_X_)		
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?			X				
Was a case-control design avoided?	X						
Did the study avoid inappropriate exclusions?			X				
Could the selection of patients have introduced bias?							X
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?			X				
If a threshold was used, was it pre-specified?				X			
Could the conduct or interpretation of the index test have introduced bias?							X
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?			X				
Were the reference standard results interpreted without knowledge of the results of the index test?			X				
Could the reference standard, its conduct, or its interpretation have introduced bias?							X
Domain 4: Flow and Timing							
Did all patients receive a reference standard?			X				
Did patients receive the same reference standard?	X						
Were all patients included in the analysis?			X				
Could the patient flow have introduced bias?							X
Comments: Limited information about patient/sample selection process, flow and timing; regarding the reference standard, as the authors describe, universal standard reference RNAs are not available for the 21 genes (their approach seems possibly reasonable, given the lack of a standard, but still raises some concern for bias).							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3461	Davidson	2013

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium		High		N/A	X
Risk of bias for KQ 4a:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
235. What is the study design?		**Uncontrolled trial**				
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
236. For RCTs, were randomization and allocation concealment adequate?					X	
237. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
238. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					Pre-post for change in decisions
239. Were groups similar at baseline?					X	1 group
240. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?		X				
241. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	X					
242. Was overall attrition less than 30%?	X					

243. Was differential attrition less than 15%?	X					
244. Does the analysis control for baseline differences between groups?					X	
245. Does the analysis account for differences in treatment received by the groups?					X	
246. Are the statistical methods used to assess the outcomes appropriate?	X					
247. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?					X	
Comments: No information reported on the number of physicians making the decisions; unclear how wide a range of decisions this represents. Article does not show what information was provided to physicians with the test results (giving just the test results vs. more information about interpretation or recommendations for treatment that could impact decisions)						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3504	De Boer	2013

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
248. What is the study design?		**Uncontrolled trial**				
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
249. For RCTs, were randomization and allocation concealment adequate?					X	
250. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
251. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
252. Were groups similar at baseline?				X		
253. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
254. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		
255. Was overall attrition less than 30%?	X					

256. Was differential attrition less than 15%?	X					
257. Does the analysis control for baseline differences between groups?		X				
258. Does the analysis account for differences in treatment received by the groups?	X					
259. Are the statistical methods used to assess the outcomes appropriate?	X					
260. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?					X	
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
4031	Delahaye	2013

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High				N/A	X
Risk of bias for KQ 2:	Low		Medium	X	High				N/A	
Risk of bias for KQ 3:	Low		Medium		High				N/A	X
Risk of bias for KQ 4a:	Low		Medium		High				N/A	X
Risk of bias for KQ 4b:	Low		Medium		High				N/A	X
Risk of bias for KQ 5:	Low		Medium		High				N/A	X
Explain any **High** ratings:										

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (_X_)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
261. What is the study design?						
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
262. For RCTs, were randomization and allocation concealment adequate?						
263. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?						
264. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?						
265. Were groups similar at baseline?						
266. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?						
267. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?						
268. Was overall attrition less than 30%?						
269. Was differential attrition less than 15%?						
270. Does the analysis control for baseline						

differences between groups?						
271. Does the analysis account for differences in treatment received by the groups?						
272. Are the statistical methods used to assess the outcomes appropriate?						
273. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?						
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?			X				
Was a case-control design avoided?	X						
Did the study avoid inappropriate exclusions?	X						
Could the selection of patients have introduced bias?					X		
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?			X				
If a threshold was used, was it pre-specified?				X			
Could the conduct or interpretation of the index test have introduced bias?							X
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?	X						
Were the reference standard results interpreted without knowledge of the results of the index test?			X				
Could the reference standard, its conduct, or its interpretation have introduced bias?					X		
Domain 4: Flow and Timing							
Did all patients receive a reference standard?			X				
Did patients receive the same reference standard?	X						
Were all patients included in the analysis?			X				
Could the patient flow have introduced bias?							X
Comments: Although some domains are unclear here, many methodological strengths described that may not be captured in this form.							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
1584	Deschoolmeester	2010

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low	*	Medium	*	High	*	N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:	Unclear risk of selection bias, ascertainment bias, and confounding							

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5 | If the study does NOT apply to any of these KQs, place an 'X' here (__)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
274. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
275. For RCTs, were randomization and allocation concealment adequate?					X	
276. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?				X		None reported; unclear how the 164 tissue samples were selected other than that they were sporadic CRC
277. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					KRAS mutation vs wild-type
278. Were groups similar at baseline?				X		No data reported for the KRAS mutation vs. wild-type groups; only reports

						overall, and separate characteristic for colon and rectum cancers
279. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?		X				
280. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		No information reported about how recurrence and death were ascertained
281. Was overall attrition less than 30%?				X		Median f/u was 4.5 years or longer, but data NR about how many subjects were missing outcome data or lost to follow up
282. Was differential attrition less than 15%?				X		
283. Does the analysis control for baseline differences between groups?				X		No baseline information reported, so unable to determine
284. Does the analysis account for differences in treatment received by the groups?				X		See comments
285. Are the statistical methods used to assess the outcomes appropriate?	X					
286. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?				X		See comments
Comments: For the multivariate analysis, it is unclear what was included. The methods report that they used a stepwise backward binary logistic regression to identify which of the clinicopathological parameters had the strongest impact on survival, but which parameters were considers is NR (possibly the things they report baseline characteristics for in Table 2: age, sex, location, grade, stage, therapy/neo-adjuvant/adjuvant, and MSI status). In the results (p 1630) they report results for multiple Cox regression analyses with age and stage.						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							

Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
477	Donada	2011

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low	x	Medium		High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
287. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
288. For RCTs, were randomization and allocation concealment adequate?					x	
289. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	x					
290. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	x					
291. Were groups similar at baseline?					x	non-randomized study, MSI+ and MSI – naturally different
292. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?		x				retrospective study, blinding not possible
293. Were outcomes assessed using valid and reliable measures, implemented consistently	x					

across all study participants?						
294. Was overall attrition less than 30%?					x	retrospective study limited to those with followup
295. Was differential attrition less than 15%?					x	
296. Does the analysis control for baseline differences between groups?	x					
297. Does the analysis account for differences in treatment received by the groups?					x	all treated with adjuvant 5FU
298. Are the statistical methods used to assess the outcomes appropriate?	x					
299. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	x					
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (___)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
180	Dowsett	2010

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
300. What is the study design?			**X**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
301. For RCTs, were randomization and allocation concealment adequate?					X	
302. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
303. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
304. Were groups similar at baseline?				X		
305. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?	X					Described in discussion
306. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		
307. Was overall attrition less than 30%?				X		
308. Was differential attrition less than 15%?				X		
309. Does the analysis control for baseline				X		

differences between groups?						
310. Does the analysis account for differences in treatment received by the groups?		X				
311. Are the statistical methods used to assess the outcomes appropriate?	X					
312. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments: Analysis adjusted for tumor size, central grade, age, and positive nodes (>=4 vs. 1-3 nodes) (essentially looked at added value of RS beyond using Adjuvant! online. Positive nodes variable was only included in analyses for N+ patients. All subjects were hormone receptor + from a trial of tamoxifen vs. anastrozole. In this study the HR for RS was similar for patients receiving either treatment and there was no significant interaction of RS with treatment arm, reducing concern that treatment differences account for findings.						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3336	Eireman	2012

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium		High		N/A	X
Risk of bias for KQ 4a:	Low	X	Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
313. What is the study design?			**X**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
314. For RCTs, were randomization and allocation concealment adequate?					X	
315. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
316. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					This is like a pre-post trst so the comparison group is the same group of pts & physicians
317. Were groups similar at baseline?					X	
318. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?	X					
319. Were outcomes assessed using valid and reliable measures, implemented consistently	X					

across all study participants?						
320. Was overall attrition less than 30%?	X					
321. Was differential attrition less than 15%?	X					
322. Does the analysis control for baseline differences between groups?					X	
323. Does the analysis account for differences in treatment received by the groups?					X	
324. Are the statistical methods used to assess the outcomes appropriate?	X					
325. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?					X	
Comments:						

Key Question 2				If study does NOT apply to this KQ, place an 'X' here (X__)			
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3548	Eklof	2013

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
326. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
327. For RCTs, were randomization and allocation concealment adequate?					X	
328. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
329. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
330. Were groups similar at baseline?		X				Differences for age, sex, site
331. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
332. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		Used Swedish population registry and patient records;

						otherwise, little information reported
333. Was overall attrition less than 30%?	X					
334. Was differential attrition less than 15%?	X					
335. Does the analysis control for baseline differences between groups?	X					
336. Does the analysis account for differences in treatment received by the groups?		X				
337. Are the statistical methods used to assess the outcomes appropriate?	X					
338. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					Final model adjusted for sex, age at diagnosis, stage, tumor site
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
501	Farina-Sarasqueta	2010

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low	X	Medium		High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
339. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
340. For RCTs, were randomization and allocation concealment adequate?					X	
341. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
342. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
343. Were groups similar at baseline?		X				observational study, patients with mutations likely naturally different
344. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?					X	
345. Were outcomes assessed using valid and reliable measures, implemented consistently	X					

across all study participants?						
346. Was overall attrition less than 30%?					X	restrospective cohort
347. Was differential attrition less than 15%?					X	retrospective cohort—limited to patients with complete records
348. Does the analysis control for baseline differences between groups?	X					
349. Does the analysis account for differences in treatment received by the groups?			X			controlled for stage, and onlystage III patients got chemotherapy
350. Are the statistical methods used to assess the outcomes appropriate?	X					
351. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (___)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3551	Feigelson	2012

Indicate the appropriate quality rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable **AND** for an Overall rating. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low	X	Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium		High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (_X_)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
352. What is the study design?						
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
353. For RCTs, were randomization and allocation concealment adequate?						
354. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?						
355. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?						
356. Were groups similar at baseline?						
357. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?						
358. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?						
359. Was overall attrition less than 30%?						
360. Was differential attrition less than 15%?						
361. Does the analysis control for baseline						

differences between groups?						
362. Does the analysis account for differences in treatment received by the groups?						
363. Are the statistical methods used to assess the outcomes appropriate?						
364. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?						
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (___)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?		X					
Was a case-control design avoided?	X						
Did the study avoid inappropriate exclusions?	X						
Could the selection of patients have introduced bias?					X		
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?				X			
If a threshold was used, was it pre-specified?				X			
Could the conduct or interpretation of the index test have introduced bias?					X		
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?	X						
Were the reference standard results interpreted without knowledge of the results of the index test?	X						
Could the reference standard, its conduct, or its interpretation have introduced bias?					X		
Domain 4: Flow and Timing							
Did all patients receive a reference standard?	X						
Did patients receive the same reference standard?	X						
Were all patients included in the analysis?	X						
Could the patient flow have introduced bias?					X		
Comments: The study was looking at inter lab concordance. So not quite sure how the questions here apply. Some differences in techniques betweebn labs and LLD is different but still achieved 90% concordance in detection. Sample size is small.							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
534	Gao	2010

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low	*	Medium	*	High	*	N/A	
Risk of bias for KQ 3:	Low		Medium		High		N/A	X
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:	Unclear risk of bias due to inadequate reporting of patient selection and other methods							

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (_X_)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
365. What is the study design?						
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
366. For RCTs, were randomization and allocation concealment adequate?						
367. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?						
368. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?						
369. Were groups similar at baseline?						
370. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?						
371. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?						
372. Was overall attrition less than 30%?						
373. Was differential attrition less than 15%?						

374. Does the analysis control for baseline differences between groups?							
375. Does the analysis account for differences in treatment received by the groups?							
376. Are the statistical methods used to assess the outcomes appropriate?							
377. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?							
Comments:							

Key Question 2					If study does NOT apply to this KQ, place an 'X' here (___)		
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?			X				
Was a case-control design avoided?	X						
Did the study avoid inappropriate exclusions?			X				
Could the selection of patients have introduced bias?							X
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?			X				
If a threshold was used, was it pre-specified?				X			
Could the conduct or interpretation of the index test have introduced bias?							X
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?	X						
Were the reference standard results interpreted without knowledge of the results of the index test?			X				
Could the reference standard, its conduct, or its interpretation have introduced bias?							X
Domain 4: Flow and Timing							
Did all patients receive a reference standard?	X						
Did patients receive the same reference standard?	X						
Were all patients included in the analysis?	X						
Could the patient flow have introduced bias?					X		
Comments: Unclear risk of bias due to incomplete reporting							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
183	Geffen	2011

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium		High		N/A	
Risk of bias for KQ 4a:	Low		Medium	x	High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
378. What is the study design?				**xx**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
379. For RCTs, were randomization and allocation concealment adequate?					x	
380. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?			x			All women tested were examined but authors acknowledge that some eligible women were not tested
381. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?					x	Pre/post comparison same subjects
382. Were groups similar at baseline?					x	Pre/post comparison
383. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?		x				

384. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?			x			Authors state they determined "pre test" recommendation on based on usual clinical practice but acknowledge this included clinical judgement, actual recommendation was not recorded before getting RS
385. Was overall attrition less than 30%?					x	
386. Was differential attrition less than 15%?					x	
387. Does the analysis control for baseline differences between groups?					x	
388. Does the analysis account for differences in treatment received by the groups?					x	
389. Are the statistical methods used to assess the outcomes appropriate?						
390. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	x					
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (X__)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							

Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
548	Geido	2002

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low	x	Medium		High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
391. What is the study design?				**x**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
392. For RCTs, were randomization and allocation concealment adequate?					x	
393. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	x					
394. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	x					
395. Were groups similar at baseline?			x			Some differences in demographics as expected for non-randomized study
396. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				x		Outcome is survival, not important
397. Were outcomes assessed using valid and	x					

reliable measures, implemented consistently across all study participants?						
398. Was overall attrition less than 30%?				x		
399. Was differential attrition less than 15%?				x		
400. Does the analysis control for baseline differences between groups?	x					
401. Does the analysis account for differences in treatment received by the groups?		x				
402. Are the statistical methods used to assess the outcomes appropriate?	x					
403. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	x					
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3411	Gligorov	2012

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium		High		N/A	X
Risk of bias for KQ 4a:	Low		Medium		High	Unclear	N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:	Unclear risk of bias; abstract only from conference; insufficient information presented to assess risk of selection bias and measurement bias.							

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (__)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
404. What is the study design?			**X**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
405. For RCTs, were randomization and allocation concealment adequate?					X	
406. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?				X		No inclusion/exclusion criteria in the abstract
407. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
408. Were groups similar at baseline?					X	It's a pre-post study of changes in decisions with/without Oncotype Dx
409. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
410. Were outcomes assessed using valid and				X		

reliable measures, implemented consistently across all study participants?						
411. Was overall attrition less than 30%?	X					
412. Was differential attrition less than 15%?	X					
413. Does the analysis control for baseline differences between groups?					X	
414. Does the analysis account for differences in treatment received by the groups?					X	
415. Are the statistical methods used to assess the outcomes appropriate?				X		
416. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?					X	
Comments: Abstract only, from conference, preliminary data on 92 of 100 subjects						

Key Question 2					If study does NOT apply to this KQ, place an 'X' here (_X_)		
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3443	Gonzalez De Castro	2012

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low	X	Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium		High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
417. What is the study design?						
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
418. For RCTs, were randomization and allocation concealment adequate?						
419. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?						
420. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?						
421. Were groups similar at baseline?						
422. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?						
423. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?						
424. Was overall attrition less than 30%?						
425. Was differential attrition less than 15%?						
426. Does the analysis control for baseline						

differences between groups?							
427. Does the analysis account for differences in treatment received by the groups?							
428. Are the statistical methods used to assess the outcomes appropriate?							
429. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?							
Comments:							

Key Question 2					If study does NOT apply to this KQ, place an 'X' here (___)		
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?	X						
Was a case-control design avoided?	X						
Did the study avoid inappropriate exclusions?			X				
Could the selection of patients have introduced bias?					X		
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?	X						
If a threshold was used, was it pre-specified?			X				
Could the conduct or interpretation of the index test have introduced bias?							X
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?	X						
Were the reference standard results interpreted without knowledge of the results of the index test?	X						
Could the reference standard, its conduct, or its interpretation have introduced bias?					X		
Domain 4: Flow and Timing							
Did all patients receive a reference standard?	X						
Did patients receive the same reference standard?	X						
Were all patients included in the analysis?	X						
Could the patient flow have introduced bias?					X		
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
579	Gryfe	2000

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
430. What is the study design?			**X**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
431. For RCTs, were randomization and allocation concealment adequate?					X	
432. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
433. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
434. Were groups similar at baseline?			X			Differences for synchronous or metachronous, location (more proximal among the MSI group), grade (more poorly

						differentiated among MSI group), and stage (fewer stage 4 in MSI group)
435. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?	X					
436. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	X					
437. Was overall attrition less than 30%?	X					
438. Was differential attrition less than 15%?	X					
439. Does the analysis control for baseline differences between groups?	X					
440. Does the analysis account for differences in treatment received by the groups?		X				Treatment differences were not included in the multivariate analysis; and information on chemo initiated within 120 days was only available for 65% of subjects
441. Are the statistical methods used to assess the outcomes appropriate?	X					
442. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					See comments below
Comments: Multivariate model obtained with step-down variable selection, in which all prognostic factors were initially entered and those with P>0.1 were rejected. Model did not include treatment differences and the outcome of the model is OS, not recurrence, so there are still a number of other potential confounders that could alter risk of death that the study does not consider (e.g., heart disease, diabetes).						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							

Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3751	Guan	2013

Indicate the appropriate quality rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable **AND** for an Overall rating. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
443. What is the study design?			**X**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
444. For RCTs, were randomization and allocation concealment adequate?					X	
445. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
446. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?			X			Some confusion in the description of the exclusion criteria which eliminated patients with EGFR mutations at exon 18 or 20 and the matched EGFR mutation group.

447. Were groups similar at baseline?	X					
448. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
449. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	X					
450. Was overall attrition less than 30%?	X					
451. Was differential attrition less than 15%?	X					
452. Does the analysis control for baseline differences between groups?	X					
453. Does the analysis account for differences in treatment received by the groups?		X				
454. Are the statistical methods used to assess the outcomes appropriate?	X					
455. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments: Primary analysis for OS did not control for treatment. Matching description a little confusing						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (___)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
581	Guidoboni	2001

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
456. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
457. For RCTs, were randomization and allocation concealment adequate?					X	
458. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
459. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
460. Were groups similar at baseline?		X				Higher proportion 60 and older, with poorly differentiated tumor, and with mucoid histological type in the MSI-H group
461. Were the outcome assessors blinded to the test result/intervention/exposure status of				X		

participants?						
462. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	X					
463. Was overall attrition less than 30%?	X					
464. Was differential attrition less than 15%?	X					
465. Does the analysis control for baseline differences between groups?		X				Other than age, the things listed above were not included in the analysis
466. Does the analysis account for differences in treatment received by the groups?		X				But a very similar proportion of subjects in both groups received adjuvant chemo
467. Are the statistical methods used to assess the outcomes appropriate?	X					
468. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					Adjusted for age, sex, and stage (and all tumors were right sided/proximal); did not adjust for grade or cellular subtypes
Comments: Small to moderate risk of measurement bias with unclear masking of outcome assessors; moderate risk of confounding with some baseline differences between groups not considered in the analysis						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have							

introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
196	Habel	2006

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low	x	Medium		High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
469. What is the study design?						
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
470. For RCTs, were randomization and allocation concealment adequate?					x	
471. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	x					
472. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	x					
473. Were groups similar at baseline?			x			Matched on age, race, tamo tx, year, facility
474. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				x		Outcome was death
475. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	x					Death determined by insurance records

476. Was overall attrition less than 30%?					x	Full f/u was a requirement for inclusion
477. Was differential attrition less than 15%?					x	
478. Does the analysis control for baseline differences between groups?	x					
479. Does the analysis account for differences in treatment received by the groups?	x					
480. Are the statistical methods used to assess the outcomes appropriate?	x					
481. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	x					
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (___)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
603	Hancer	2011

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low	*	Medium	*	High	*	N/A	
Risk of bias for KQ 3:	Low		Medium		High		N/A	X
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:	*Overall, unclear risk of bias due to inadequate reporting							

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (_X_)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
482. What is the study design?						
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
483. For RCTs, were randomization and allocation concealment adequate?						
484. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?						
485. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?						
486. Were groups similar at baseline?						
487. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?						
488. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?						
489. Was overall attrition less than 30%?						
490. Was differential attrition less than 15%?						
491. Does the analysis control for baseline						

differences between groups?							
492. Does the analysis account for differences in treatment received by the groups?							
493. Are the statistical methods used to assess the outcomes appropriate?							
494. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?							
Comments:							

Key Question 2					If study does NOT apply to this KQ, place an 'X' here (___)		
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?			X				
Was a case-control design avoided?	X						
Did the study avoid inappropriate exclusions?			X				
Could the selection of patients have introduced bias?							X
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?			X				
If a threshold was used, was it pre-specified?			X				
Could the conduct or interpretation of the index test have introduced bias?							X
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?	X						
Were the reference standard results interpreted without knowledge of the results of the index test?			X				
Could the reference standard, its conduct, or its interpretation have introduced bias?							X
Domain 4: Flow and Timing							
Did all patients receive a reference standard?	X						
Did patients receive the same reference standard?	X						
Were all patients included in the analysis?	X						
Could the patient flow have introduced bias?					X		
Comments: Overall, unclear risk of bias due to inadequate reporting							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
137	Henry	2009

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium		High		N/A	
Risk of bias for KQ 4a:	Low	x	Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
495. What is the study design?						**x**
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
496. For RCTs, were randomization and allocation concealment adequate?					x	
497. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	x					
498. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	x					pre-post test design: pre-test decisions compared to post-test decisions
499. Were groups similar at baseline?	x					same patients pre/post
500. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?			x			blinded for pre test
501. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	x					

502. Was overall attrition less than 30%?						x	
503. Was differential attrition less than 15%?						x	
504. Does the analysis control for baseline differences between groups?						x	
505. Does the analysis account for differences in treatment received by the groups?						x	
506. Are the statistical methods used to assess the outcomes appropriate?	x						descriptive statistics only
507. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?							
Comments:							

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
2051	Hiramatsu	2010

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium		High	X	N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:	High risk of selection bias, ascertainment bias, and confounding.							

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
508. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
509. For RCTs, were randomization and allocation concealment adequate?					X	
510. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?				X		Methods of selecting included cases NR
511. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					Probably, but methods of selecting the full sample are not described
512. Were groups similar at baseline?				X		Baseline data are not reported by mutation status
513. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		

514. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		No methods reported for how the prognostic outcomes were defined or ascertained
515. Was overall attrition less than 30%?		X				
516. Was differential attrition less than 15%?				X		
517. Does the analysis control for baseline differences between groups?				X		
518. Does the analysis account for differences in treatment received by the groups?		X				
519. Are the statistical methods used to assess the outcomes appropriate?	X					
520. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments: High risk of selection bias, ascertainment bias, and confounding. Methods of selecting the 193 lung cancer cases NR; only evaluated EGFR and KRAS mutation status for 93/193 (48%) and reasons for selecting those 93 were NR; no description of how outcomes were defined or ascertained (it is described in the results as "survival", but unclear if it is disease-specific or overall survival; but seems more likely overall survival); analyses don't account for differences in treatment received.						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3507	Holt	2013

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium		High		N/A	X
Risk of bias for KQ 4a:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
521. What is the study design?		**Uncontrolled trial**				
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
522. For RCTs, were randomization and allocation concealment adequate?					X	
523. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
524. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
525. Were groups similar at baseline?				X		
526. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
527. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		
528. Was overall attrition less than 30%?	X					

529. Was differential attrition less than 15%?	X					
530. Does the analysis control for baseline differences between groups?		X				
531. Does the analysis account for differences in treatment received by the groups?	X					
532. Are the statistical methods used to assess the outcomes appropriate?	X					
533. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?					X	
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
630	Hong	2012

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
534. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
535. For RCTs, were randomization and allocation concealment adequate?					X	
536. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
537. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
538. Were groups similar at baseline?		X				Differences for age, family history, stage, tumor type (colon or rectum), site of tumor, grade, CEA level
539. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		

540. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		
541. Was overall attrition less than 30%?	X					
542. Was differential attrition less than 15%?	X					
543. Does the analysis control for baseline differences between groups?			X			Controls for age, sex, stage
544. Does the analysis account for differences in treatment received by the groups?		X				Table 5 shows additional analysis stratified by whether they got 5-FU chemo, but these are set up to focus on prediction, not to adjust for differences in treatment within the multivariate analysis of MSI-H vs. MSS/MSI-L (and nothing to account for radiation)
545. Are the statistical methods used to assess the outcomes appropriate?	X					
546. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?			X			It controls for age, sex, stage, but not for grade, cellular type, CEA, location; they also stratify colon and rectal cancers
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced							

bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments: Overall, unclear risk of bias due to inadequate reporting							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
1621	Imamura	2012

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium		High	X	N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
547. What is the study design?			**X**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
548. For RCTs, were randomization and allocation concealment adequate?					X	
549. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
550. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
551. Were groups similar at baseline?		X				Baseline differences for sex, tumor location, stage, differentiation, MSI status
552. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
553. Were outcomes assessed using valid and	X					

reliable measures, implemented consistently across all study participants?						
554. Was overall attrition less than 30%?				X		
555. Was differential attrition less than 15%?				X		
556. Does the analysis control for baseline differences between groups?	X					
557. Does the analysis account for differences in treatment received by the groups?		X				
558. Are the statistical methods used to assess the outcomes appropriate?	X					
559. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?				X		Unable to determine what was in the final model. They report what went into the initial model, and process for selecting final model (but not what was in it)
Comments: High risk of selection bias and confounding. The variables in the final model were not reported, but the process described for selecting the variables seems reasonable. The article reports that the regression model was stage-stratified, but the results reported in Table 3 and in the text are not stage-stratified (there is just one HR for codon 12 mutants and one for codon 13 mutants for each outcome); so it is unclear that the HRs reported did anything to account for stage. Given these issues, high risk of confounding bias. With the codon 12 mutants found to have HRs just above 1 (1.30 and 1.24 for cancer-specific mortality and overall mortality), the findings might become non-significant with relatively minor changes in what was adjusted for in the model, and how stage was handled.						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							

Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3281	Iwamoto	2011

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

RoB Rating: Unclear

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low	*	Medium	*	High	*	N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (__)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
560. What is the study design?			**X**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
561. For RCTs, were randomization and allocation concealment adequate?					X	
562. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?				X		
563. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
564. Were groups similar at baseline?				X		
565. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
566. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		
567. Was overall attrition less than 30%?				X		

568. Was differential attrition less than 15%?				X		
569. Does the analysis control for baseline differences between groups?				X		
570. Does the analysis account for differences in treatment received by the groups?					X	From description, all got same treatment
571. Are the statistical methods used to assess the outcomes appropriate?	X					
572. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3456	Jancik	2012

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High	H	N/A	
Risk of bias for KQ 3:	Low		Medium		High		N/A	X
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (_X_)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
573. What is the study design?						
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
574. For RCTs, were randomization and allocation concealment adequate?						
575. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?						
576. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?						
577. Were groups similar at baseline?						
578. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?						
579. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?						
580. Was overall attrition less than 30%?						
581. Was differential attrition less than 15%?						
582. Does the analysis control for baseline						

differences between groups?							
583. Does the analysis account for differences in treatment received by the groups?							
584. Are the statistical methods used to assess the outcomes appropriate?							
585. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?							
Comments:							

Key Question 2					If study does NOT apply to this KQ, place an 'X' here (___)		
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?			X				
Was a case-control design avoided?	X						
Did the study avoid inappropriate exclusions?	X						
Could the selection of patients have introduced bias?					X		
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?	X						
If a threshold was used, was it pre-specified?	X						
Could the conduct or interpretation of the index test have introduced bias?					X		
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?	X						
Were the reference standard results interpreted without knowledge of the results of the index test?	X						
Could the reference standard, its conduct, or its interpretation have introduced bias?					X		
Domain 4: Flow and Timing							
Did all patients receive a reference standard?	X						
Did patients receive the same reference standard?	X						
Were all patients included in the analysis?	X						
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
673	Jensen	2009

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
586. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
587. For RCTs, were randomization and allocation concealment adequate?					X	
588. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
589. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
590. Were groups similar at baseline?		X				Differences for age, tumor site, grade, and bowel obstruction
591. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
592. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?			X			Yes for death, unclear for recurrence (used

						databases on hospital admission)
593. Was overall attrition less than 30%?	X					
594. Was differential attrition less than 15%?	X					
595. Does the analysis control for baseline differences between groups?			X			Initial model reported to include all candidate prognostic variables; final model did not include age, site, grade (and all were different at baseline)
596. Does the analysis account for differences in treatment received by the groups?					X	All received same adjuvant treatment
597. Are the statistical methods used to assess the outcomes appropriate?	X					
598. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?		X				Final model adjusted for stage, vascular invasion, perineural invasion, and ileus.
Comments: Final model adjusted for stage, vascular invasion, perineural invasion, and ileus. Initial model reported to include all candidate prognostic variables (but they don't report what that full list included), and they used step-down variable selection; final model did not include age, site, grade (and all were different in baseline characteristics) or cellular subtypes (NR at baseline or as something included in models) or sex.						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have							

introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
110	Joh	2011

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium		High		N/A	
Risk of bias for KQ 4a:	Low	x	Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
599. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
600. For RCTs, were randomization and allocation concealment adequate?					X	
601. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
602. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	x					
603. Were groups similar at baseline?		x				would not be expected to be similar in retrospective design
604. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?	x					
605. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?						

606. Was overall attrition less than 30%?					x	
607. Was differential attrition less than 15%?					x	
608. Does the analysis control for baseline differences between groups?					x	
609. Does the analysis account for differences in treatment received by the groups?					x	
610. Are the statistical methods used to assess the outcomes appropriate?	x					
611. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?					x	
Comments: Study was a survey of providers regarding treatment recommendations with or without information from the oncotype test. Answered these questions with patients as "participants" and providers as "assessors" since no comparative data were given regarding demographics of the small # of providers in the study.						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
691	Kakar	2008

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium		High	X	N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:	High risk of selection bias and confounding. Small sample size and it's unclear how subjects were selected from among those undergoing resection from 1996 to 2000 (NR whether consecutive or what the criteria were). Some baseline differences between groups and some known prognostic factors were not considered in the analyses (i.e., multivariate analysis did not adjust for some important factors). Just 10 subjects with BRAF mutation. Unable to assess potential for measurement bias because little information reported. The magnitude of benefit is large (HR above 5), but with such a small sample size, still high risk of confounding.							

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (__)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
612. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
613. For RCTs, were randomization and allocation concealment adequate?					X	
614. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?				X		
615. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?				X		
616. Were groups similar at baseline?			X			Similar for sex, age, all were MSS; higher proportion of

						those with BRAF mutation (than those without BRAF mutation) had right sided cancer and stage III or IV cancer
617. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
618. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		
619. Was overall attrition less than 30%?				X		
620. Was differential attrition less than 15%?				X		
621. Does the analysis control for baseline differences between groups?			X			Not for differences in tumor location
622. Does the analysis account for differences in treatment received by the groups?		X				
623. Are the statistical methods used to assess the outcomes appropriate?	X					
624. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?			X			Adjusted for age, sex, stage; did not adjust for grade, cellular subtypes, lymphovascular invastion, location, margin status
Comments:						

Key Question 2				If study does NOT apply to this KQ, place an 'X' here (_X_)			
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have							

introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
693	Kalady	2012

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
625. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
626. For RCTs, were randomization and allocation concealment adequate?					X	
627. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?				X		Unclear how they got from 475 included subjects down to 322 to include in the analyses (59 were not included because they were stage 4, but another 94 that were not included)
628. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
629. Were groups similar at baseline?		X				Differences for age, sex,

						location, differentiation, MSI status
630. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
631. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		No information reported for how outcomes were ascertained
632. Was overall attrition less than 30%?		X				23% of Stage I to III subjects were not included in the survival analyses
633. Was differential attrition less than 15%?				X		NR
634. Does the analysis control for baseline differences between groups?	X					
635. Does the analysis account for differences in treatment received by the groups?		X				
636. Are the statistical methods used to assess the outcomes appropriate?	X					
637. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments: 475 included in Table 1, but just 322 included in the survival analyses (related to comments above). Note: Included for KQ3 only and for BRAF only--MSI used the 10 marker panel						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							

Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
170	Kamal	2011

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium		High		N/A	X
Risk of bias for KQ 4a:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
638. What is the study design?						Other: uncontrolled trial
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
639. For RCTs, were randomization and allocation concealment adequate?					X	
640. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?					X	study did not form comparison groups for the subjects (the 6 oncologists are the subjects)
641. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?					X	
642. Were groups similar at baseline?					X	
643. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?					X	
644. Were outcomes assessed using valid and				X		Details NR

reliable measures, implemented consistently across all study participants?						about how they really gathered data on the oncologists decisions
645. Was overall attrition less than 30%?	X					
646. Was differential attrition less than 15%?	X					
647. Does the analysis control for baseline differences between groups?					X	
648. Does the analysis account for differences in treatment received by the groups?					X	
649. Are the statistical methods used to assess the outcomes appropriate?	X					
650. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?					X	
Comments: uncontrolled trial evaluating whether 6 medical oncologists would change treatment recommendations when given Oncotype Dx RS result in addition to information about standard demographic and tumor prognostic criteria (as opposed to just being given standard prognostic criteria); some risk of measurement bias (no detailed description of how they gathered outcomes; unlike some other studies that used a formal questionnaire, this sounds less formal and perhaps more subject to social desirability bias, ascertainment bias); relatively small sample (6 oncologists) and no information provided about those 6 (e.g., whether they were from multiple centers or just from 1 group with like-minded approach)						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3369	Kamat	2011

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low	X	Medium		High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
651. What is the study design?			**X**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
652. For RCTs, were randomization and allocation concealment adequate?					X	
653. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
654. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
655. Were groups similar at baseline?					X	
656. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
657. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	X					
658. Was overall attrition less than 30%?	X					
659. Was differential attrition less than 15%?	X					
660. Does the analysis control for baseline					X	

differences between groups?						
661. Does the analysis account for differences in treatment received by the groups?					X	
662. Are the statistical methods used to assess the outcomes appropriate?	X					
663. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments:						

Key Question 2					If study does NOT apply to this KQ, place an 'X' here (X__)		
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
715	Kim	2007

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	x
Risk of bias for KQ 2:	Low		Medium		High		N/A	x
Risk of bias for KQ 3:	Low	x	Medium		High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	x
Risk of bias for KQ 4b:	Low		Medium		High		N/A	x
Risk of bias for KQ 5:	Low		Medium		High		N/A	x
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
664. What is the study design?				**x**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
665. For RCTs, were randomization and allocation concealment adequate?					x	
666. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	x					
667. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	x					
668. Were groups similar at baseline?				x		
669. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?	x					
670. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	x					
671. Was overall attrition less than 30%?	x					
672. Was differential attrition less than 15%?	x					
673. Does the analysis control for baseline				x		Since

differences between groups?						baseline differences not reported
674. Does the analysis account for differences in treatment received by the groups?	x					
675. Are the statistical methods used to assess the outcomes appropriate?						
676. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	x					
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (___)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
2165	Kim	2008

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
677. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
678. For RCTs, were randomization and allocation concealment adequate?					X	
679. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					Criteria were that they underwent surgical resection for primary lung cancer between Dec 2000 and Apr 2004 at their University Hospital, path diagnosis of lung adenocarcinoma, and frozen specimens available

680. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
681. Were groups similar at baseline?		X (for EGFR mutation status)		X (for KRAS)		Table 2 only provided gender, age, smoking, BAC features, and stage for EGFR status (some differences for gender, smoking status, and BAC); information is NR for KRAS
682. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?		X				
683. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?			X			Methods of detecting recurrence seem valid and reliable; for deaths, no description of methods to ensure capturing all deaths (and article does not describe completeness of follow up)
684. Was overall attrition less than 30%?				X		Missing data and loss to follow up not described in detail for the 71 patients (mean f/u was 25.3 months, range 2.9 to 47.5)
685. Was differential attrition less than 15%?				X		
686. Does the analysis control for baseline differences between groups?	X					
687. Does the analysis account for differences in treatment received by the groups?		X				
688. Are the statistical methods used to assess the outcomes appropriate?	X					
689. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					Most
Comments: no details reported for reasons that most of the 653 patients who underwent surgical resection from primary lung cancer were not included; 71 were included in this study (perhaps availability of frozen specimens was the main reason)						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?	

	Yes	No	Unclear	NA	Low	High	Unclear
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3784	Kim	2013

Indicate the appropriate quality rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable **AND** for an Overall rating. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
690. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
691. For RCTs, were randomization and allocation concealment adequate?					X	
692. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
693. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
694. Were groups similar at baseline?		X				
695. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
696. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		
697. Was overall attrition less than 30%?	X					
698. Was differential attrition less than 15%?	X					
699. Does the analysis control for baseline	X					

differences between groups?						
700. Does the analysis account for differences in treatment received by the groups?		X				
701. Are the statistical methods used to assess the outcomes appropriate?	X					
702. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments: Do not seem to have controlled for size, differentiation but do not think that introduces much bias.						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (___)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
140	Klang	2010

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium		High		N/A	
Risk of bias for KQ 4a:	Low	x	Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
703. What is the study design?						**x**
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
704. For RCTs, were randomization and allocation concealment adequate?						
705. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	x					
706. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	x					pre-post test design
707. Were groups similar at baseline?					x	case series
708. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?	x					pre-post design, did not know results in pretest
709. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	x					
710. Was overall attrition less than 30%?					x	
711. Was differential attrition less than 15%?					x	

712. Does the analysis control for baseline differences between groups?					x	
713. Does the analysis account for differences in treatment received by the groups?	x					
714. Are the statistical methods used to assess the outcomes appropriate?	x					
715. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?						
Comments: The parent study is a cost effectiveness analysis (none of the listed study designs), but case scenarios from 300+ consecutive patients were used to generate estimates so I call it a case series.						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
179	Knauer	2010

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
716. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
717. For RCTs, were randomization and allocation concealment adequate?					X	
718. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
719. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
720. Were groups similar at baseline?				X		
721. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
722. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		
723. Was overall attrition less than 30%?				X		
724. Was differential attrition less than 15%?				X		
725. Does the analysis control for baseline				X		

differences between groups?						
726. Does the analysis account for differences in treatment received by the groups?	X					
727. Are the statistical methods used to assess the outcomes appropriate?	X					
728. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					

Comments: For the study design, they defined their cohort as a subset (unilateral stage pT1 to 3, HER-2 positive, etc.) of a database comprised of subjects from previous studies. Medium or greater risk of measurement bias (no information presented about whether assessment of outcomes was equal, valid, and reliable) and whether outcome assessors were aware of test results. Difficult to assess selection bias and confounding since they don't report attrition data (overall or differential) or baseline characteristics for the two groups separately. But, their multivariate analysis does account for most or all of the standard prognostic markers, decreasing the concern for confounding somewhat. Was on the fence between medium and high risk of bias, but went with medium for this.

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
2176	Kobayashi	2008

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium	X	High		N/A	X
Risk of bias for KQ 3:	Low		Medium		High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
729. What is the study design?						
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
730. For RCTs, were randomization and allocation concealment adequate?					X	
731. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
732. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
733. Were groups similar at baseline?		X				Table 2 doesn't report all the numbers and percents for the wild-type group to easily compare them, but they give enough information to

						do the calculations ourselves; groups were different for sex and smoking status at baseline, similar for age CEA level, tumor size (all were same Stage)
734. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
735. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?			X			If people continued to follow up as planned, then the measures are valid and reliable. But, nothing additional done to ensure capturing all deaths beyond using data from scheduled routine follow up (and from the f/u information reported, unable to determine how many subjects only had 1 to 3 years of follow up time captured).
736. Was overall attrition less than 30%?				X		Median f/u among surviving patients 67 months (range 12-134 months); loss to follow up details otherwise NR.
737. Was differential attrition less than 15%?				X		Data NR to allow determination
738. Does the analysis control for baseline differences between groups?	X					
739. Does the analysis account for differences in treatment received by the groups?	X					Since all were Stage IA and <20mm,

						treatment was surgical without chemo or radiotherapy
740. Are the statistical methods used to assess the outcomes appropriate?	X					
741. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					All were stage IA; analyses adjust for age, sex, smoking status, CEA, tumor size, Non-BAC component, and EGFR
Comments: some concern for selection bias, adequacy of follow up information (missing data), and ascertainment bias						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
741	Kobunai	2010

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low	X	Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium		High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (X__)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
742. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
743. For RCTs, were randomization and allocation concealment adequate?						
744. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?						
745. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?						
746. Were groups similar at baseline?						
747. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?						
748. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?						
749. Was overall attrition less than 30%?						
750. Was differential attrition less than 15%?						
751. Does the analysis control for baseline						

differences between groups?							
752. Does the analysis account for differences in treatment received by the groups?							
753. Are the statistical methods used to assess the outcomes appropriate?							
754. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?							
Comments:							

Key Question 2					If study does NOT apply to this KQ, place an 'X' here (___)		
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?			X				
Was a case-control design avoided?	X						
Did the study avoid inappropriate exclusions?	X						
Could the selection of patients have introduced bias?					X		
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?	X						
If a threshold was used, was it pre-specified?	X						
Could the conduct or interpretation of the index test have introduced bias?					X		
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?			X				
Were the reference standard results interpreted without knowledge of the results of the index test?	X						
Could the reference standard, its conduct, or its interpretation have introduced bias?							X
Domain 4: Flow and Timing							
Did all patients receive a reference standard?	X						
Did patients receive the same reference standard?	X						
Were all patients included in the analysis?	X						
Could the patient flow have introduced bias?					X		
Comments: it is unclear in this paper which is the reference standard – direct sequencing is generally thought of as a standard, but the alternative test (real time PCR using PNA clamping) appears to be more sensitive							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
2180	Koh	2010

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium		High	x	N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
755. What is the study design?				**x**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
756. For RCTs, were randomization and allocation concealment adequate?					x	
757. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	x					
758. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	x					
759. Were groups similar at baseline?				x		Demographics not reported by EGFR status
760. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?		x				Outcome is death
761. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?						Outcome is death
762. Was overall attrition less than 30%?					X	

763. Was differential attrition less than 15%?					X	
764. Does the analysis control for baseline differences between groups?	X					
765. Does the analysis account for differences in treatment received by the groups?		X				Excluded patients who got chemo
766. Are the statistical methods used to assess the outcomes appropriate?	X					
767. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	x					
Comments: methods of measuring EGFR not described. % of sample with EGFR mutations not described, limiting the ability to determine whether sample size is a problem. Also unclear how the inclusion of novel markers with uncertain interactions with EGFR positivity in the model would change the effect size/direction with respect to EGFR.						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3600	Li	2012

Indicate the appropriate quality rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable **AND** for an Overall rating. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (__)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
768. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
769. For RCTs, were randomization and allocation concealment adequate?					X	
770. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
771. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
772. Were groups similar at baseline?		X				
773. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?		X				
774. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		Ascertainment methods NR
775. Was overall attrition less than 30%?	X					
776. Was differential attrition less than 15%?	X					
777. Does the analysis control for baseline	X					

differences between groups?						
778. Does the analysis account for differences in treatment received by the groups?					X	All received same treatment
779. Are the statistical methods used to assess the outcomes appropriate?	X					
780. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (___)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
843	Lin	2011

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
781. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
782. For RCTs, were randomization and allocation concealment adequate?					X	
783. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
784. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
785. Were groups similar at baseline?		X				Differences for histology, mucin-containing tumors, location (proximal), sex, and stage
786. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		

787. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		
788. Was overall attrition less than 30%?	X					Follow up was 98% for at least 3 years (not certain beyond 3 years)
789. Was differential attrition less than 15%?	X					
790. Does the analysis control for baseline differences between groups?			X			Yes, for the variables listed below; no for mucinous component, location (proximal or distal), but those were NS in the univariate
791. Does the analysis account for differences in treatment received by the groups?		X				
792. Are the statistical methods used to assess the outcomes appropriate?	X					
793. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					Most, not all
Comments: Some risk of measurement bias and confounding. Not large effect size in multivariate analyses for OS (the only one that remained statistically significant). Possible that it also would have been NS with further adjustment for other potential confounders.						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							

Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
851	Liou	2011

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
794. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
795. For RCTs, were randomization and allocation concealment adequate?					X	
796. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
797. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
798. Were groups similar at baseline?		X				For the KRAS groups, differences for smoking, age, BMI, alcohol drinking, DM, and location of cancer (proximal vs. distal). For the BRAF groups,

						differences for location of cancer, differentiation.
799. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?		X				
800. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	X			X		Death ascertained by National Taiwan Mortality Registry. It was equal, probably valid and reliable for death/overall survival, but uncertain if it is valid and reliable to determine cause of death (for cancer-specific death outcomes)
801. Was overall attrition less than 30%?	X					Exact attrition data NR, but median followup range was from 49 to 82 months (suggesting that they had at least 4 years of follow up for all subjects)
802. Was differential attrition less than 15%?	X					
803. Does the analysis control for baseline differences between groups?			X			
804. Does the analysis account for differences in treatment received by the groups?		X				Yes for KRAS for OS, but no for BRAF analyses. But, more than 85% of patients for whom adjuvant chemo was indicated (stage 3 or 4) got the same regimen—5FU, LV, and oxaliplatin; the other 15% got 5FU and LV.
805. Are the statistical methods used to assess	X					

the outcomes appropriate?						
806. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					For BRAF, adjusted for age, sex, stage, lymphatic invasion, venous invasion, tumor differentiation, CEA level (>5 vs. ≤5 ng/mL); For KRAS overall survival analysis: age, sex, stage, use of adjuvant chemotherapy
Comments: Moderate risk of selection bias, measurement bias, and confounding						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
2249	Liu	2010

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium	x	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
807. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
808. For RCTs, were randomization and allocation concealment adequate?					X	
809. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
810. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
811. Were groups similar at baseline?				x		Detailed demographics by group not reported
812. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?		X				Outcome is survival
813. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	x					Outcome is survival
814. Was overall attrition less than 30%?					X	

815. Was differential attrition less than 15%?					X	
816. Does the analysis control for baseline differences between groups?	X					
817. Does the analysis account for differences in treatment received by the groups?		x				Some pts received radiation or chemo and these were not controlled for
818. Are the statistical methods used to assess the outcomes appropriate?	X					
819. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (X__)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
175	Lo	2010

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium		High		N/A	X
Risk of bias for KQ 4a:	Low	X	Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
820. What is the study design?						Other, design is an uncontrolled trial
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
821. For RCTs, were randomization and allocation concealment adequate?					X	
822. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?					X	Just one group
823. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?					X	
824. Were groups similar at baseline?					X	
825. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?					X	
826. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	X					
827. Was overall attrition less than 30%?	X					

828. Was differential attrition less than 15%?	X					
829. Does the analysis control for baseline differences between groups?					X	
830. Does the analysis account for differences in treatment received by the groups?					X	
831. Are the statistical methods used to assess the outcomes appropriate?	X					
832. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?					X	
Comments: uncontrolled trial (with the intervention being giving the oncologists the Oncotype Dx information) evaluating whether Oncotype Dx information changes decisions. Good that they attempted to get oncologists from several centers (4 centers in 3 different states—California, Michigan, Illinois) to avoid just representing the opinion of 1 group. Formal questionnaire to assess treatment recommendations and confidence in those recommendations.						

Key Question 2					If study does NOT apply to this KQ, place an 'X' here (_X_)		
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3605	Lochhead	2013

Indicate the appropriate quality rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable **AND** for an Overall rating. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
833. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
834. For RCTs, were randomization and allocation concealment adequate?					X	
835. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
836. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
837. Were groups similar at baseline?		X				
838. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
839. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?			X			National Death Index is valid and reliable for all-cause mortality, but it is not clear

						whether having the study physicians determine the cause of death is valid and reliable for cancer-specific mortality
840. Was overall attrition less than 30%?	X					
841. Was differential attrition less than 15%?	X					
842. Does the analysis control for baseline differences between groups?	X					
843. Does the analysis account for differences in treatment received by the groups?		X				
844. Are the statistical methods used to assess the outcomes appropriate?	X					
845. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (___)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3458	Lopez-Rios	2012

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low	X	Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium		High		N/A	X
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (_X_)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
846. What is the study design?						
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
847. For RCTs, were randomization and allocation concealment adequate?						
848. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?						
849. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?						
850. Were groups similar at baseline?						
851. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?						
852. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?						
853. Was overall attrition less than 30%?						
854. Was differential attrition less than 15%?						
855. Does the analysis control for baseline						

differences between groups?							
856. Does the analysis account for differences in treatment received by the groups?							
857. Are the statistical methods used to assess the outcomes appropriate?							
858. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?							
Comments:							

Key Question 2					If study does NOT apply to this KQ, place an 'X' here (___)		
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?		X					
Was a case-control design avoided?	x						
Did the study avoid inappropriate exclusions?	X						
Could the selection of patients have introduced bias?					X		
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?	X						
If a threshold was used, was it pre-specified?	X						
Could the conduct or interpretation of the index test have introduced bias?					X		
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?	x						
Were the reference standard results interpreted without knowledge of the results of the index test?	x						
Could the reference standard, its conduct, or its interpretation have introduced bias?					x		
Domain 4: Flow and Timing							
Did all patients receive a reference standard?	x						
Did patients receive the same reference standard?	x						
Were all patients included in the analysis?	x						
Could the patient flow have introduced bias?					x		
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
883	Maestro	2007

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
859. What is the study design?			**X**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
860. For RCTs, were randomization and allocation concealment adequate?					X	
861. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
862. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
863. Were groups similar at baseline?			X			Some differences for site of tumor, sex
864. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		Not reported
865. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		No details reported of how they determined deaths, and

						which were a consequence of the tumor (which is what they analyzed)
866. Was overall attrition less than 30%?	X					Just 1 lost to followup
867. Was differential attrition less than 15%?	X					
868. Does the analysis control for baseline differences between groups?	X					
869. Does the analysis account for differences in treatment received by the groups?	X					
870. Are the statistical methods used to assess the outcomes appropriate?	X					
871. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments: Moderate risk of measurement bias; no reporting of masking of outcome assessors; no reporting of methods of ascertainment.						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
2267	Mak	2011

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
872. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
873. For RCTs, were randomization and allocation concealment adequate?					X	
874. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
875. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
876. Were groups similar at baseline?		X				Differences for smoking status, Stage, tumor size, radiotherapy treatment mode, and whether they had surgical resection of the primary tumor.

877. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?		X				
878. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?			X			The definitions of the outcomes are reasonable, but unclear whether reviewing their medical records provided valid and reliable assessments of recurrence and survival; unclear how complete the data was from their medical record review (e.g., how many patients lacked complete f/u or went to other hospitals). No description of methods to ensure capturing deaths.
879. Was overall attrition less than 30%?				X		
880. Was differential attrition less than 15%?				X		
881. Does the analysis control for baseline differences between groups?	X					
882. Does the analysis account for differences in treatment received by the groups?	X					
883. Are the statistical methods used to assess the outcomes appropriate?	X					
884. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					Final model didn't have most of them, but they started with considering most of them, and used appropriate stepwise selection to determine those in the final model.
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)

KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
176	Mamounas	2010

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
885. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
886. For RCTs, were randomization and allocation concealment adequate?					X	
887. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
888. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
889. Were groups similar at baseline?				X		
890. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
891. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		The 2 RCTs that they obtained subjects from might have more description of

						how LRR was determined
892. Was overall attrition less than 30%?				X		
893. Was differential attrition less than 15%?				X		
894. Does the analysis control for baseline differences between groups?				X		
895. Does the analysis account for differences in treatment received by the groups?	X					
896. Are the statistical methods used to assess the outcomes appropriate?	X					
897. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments: multivariate adjusted analysis included age, tumor size, tumor grade, and treatment differences (all subjects were node negative and ER+ so those did not need to be considered)						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3415	Mamounas	2012

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium		High	Unclear	N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:	Unclear risk of bias; abstract only from conference; insufficient information presented to assess risk of selection bias, confounding, and measurement bias.							

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (__)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
898. What is the study design?			**X**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
899. For RCTs, were randomization and allocation concealment adequate?					X	
900. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?				X		
901. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
902. Were groups similar at baseline?				X		
903. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
904. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		
905. Was overall attrition less than 30%?				X		
906. Was differential attrition less than 15%?				X		

907. Does the analysis control for baseline differences between groups?				X			
908. Does the analysis account for differences in treatment received by the groups?	X						
909. Are the statistical methods used to assess the outcomes appropriate?				X			
910. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X						
Comments:							

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
1653	Mancini	2010

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium	X	High		N/A	
Risk of bias for KQ 3:	Low		Medium		High		N/A	X
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (_X_)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
911. What is the study design?						
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
912. For RCTs, were randomization and allocation concealment adequate?						
913. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?						
914. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?						
915. Were groups similar at baseline?						
916. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?						
917. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?						
918. Was overall attrition less than 30%?						
919. Was differential attrition less than 15%?						
920. Does the analysis control for baseline						

differences between groups?						
921. Does the analysis account for differences in treatment received by the groups?						
922. Are the statistical methods used to assess the outcomes appropriate?						
923. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?						
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (___)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?	X						
Was a case-control design avoided?	X						
Did the study avoid inappropriate exclusions?	X						
Could the selection of patients have introduced bias?					X		
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?			X				
If a threshold was used, was it pre-specified?	X						
Could the conduct or interpretation of the index test have introduced bias?							X
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?	X						
Were the reference standard results interpreted without knowledge of the results of the index test?			X				
Could the reference standard, its conduct, or its interpretation have introduced bias?							X
Domain 4: Flow and Timing							
Did all patients receive a reference standard?	X						
Did patients receive the same reference standard?	X						
Were all patients included in the analysis?	X						
Could the patient flow have introduced bias?					X		
Comments: For the aspects that were reported, risk of bias seems low. Although it is not clear whether the various tests were interpreted without knowledge of the reference standard result and vice versa, the article implies that there was no masking of outcome assessors to the results of the other tests.							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
2288	Matsumoto	2005

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium	x	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
924. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
925. For RCTs, were randomization and allocation concealment adequate?					X	
926. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
927. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
928. Were groups similar at baseline?		x				Not expected in nonrandomized study
929. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				x		Outcome is death, not relevant
930. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	x					
931. Was overall attrition less than 30%?				X		

932. Was differential attrition less than 15%?				X		
933. Does the analysis control for baseline differences between groups?	X					
934. Does the analysis account for differences in treatment received by the groups?		x				All pts treated pretty similarly
935. Are the statistical methods used to assess the outcomes appropriate?	X					
936. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments: my only concern regarding this paper is the sample size, confidence interval was quite wide for main effect of interest. Also, restricted to stage I cancers which have an overall very good prognosis, should not generalize to the entire stage I-III population						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
133	Mook	2009

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low	X	Medium		High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
937. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
938. For RCTs, were randomization and allocation concealment adequate?					X	
939. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
940. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
941. Were groups similar at baseline?		X				not expected in a retrospective observational design
942. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?					X	
943. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	X					

944. Was overall attrition less than 30%?				X		
945. Was differential attrition less than 15%?				X		
946. Does the analysis control for baseline differences between groups?	X					
947. Does the analysis account for differences in treatment received by the groups?	X					
948. Are the statistical methods used to assess the outcomes appropriate?	X					
949. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments:							

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
109	Mook	2010

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low	X	Medium		High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
950. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
951. For RCTs, were randomization and allocation concealment adequate?					X	
952. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?		X				pooled analysis of 7 cohorts with slightly different criteria
953. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
954. Were groups similar at baseline?		X				in non RCT comparison groups would not be expected to be similar
955. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?					X	

956. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	X					
957. Was overall attrition less than 30%?				X		
958. Was differential attrition less than 15%?				X		
959. Does the analysis control for baseline differences between groups?	X					
960. Does the analysis account for differences in treatment received by the groups?	X					
961. Are the statistical methods used to assess the outcomes appropriate?	X					
962. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (___)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
156	Mook	2010

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
963. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
964. For RCTs, were randomization and allocation concealment adequate?					x	
965. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	x					
966. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?			x			
967. Were groups similar at baseline?				x		
968. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?					x	
969. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	x					
970. Was overall attrition less than 30%?				x		
971. Was differential attrition less than 15%?				x		
972. Does the analysis control for baseline		x				used a

differences between groups?						composite of common prognostic factors including age and overall health, but do not appear to have adjusted for other baseline differences
973. Does the analysis account for differences in treatment received by the groups?		x				
974. Are the statistical methods used to assess the outcomes appropriate?	x					
975. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?						see above, did not control separately for prognostic variables, used a composite score
Comments:						

Key Question 2					If study does NOT apply to this KQ, place an 'X' here (_X_)		
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
2342	Naoki	2011

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low	x	Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium		High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (_x_)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
976. What is the study design?						
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
977. For RCTs, were randomization and allocation concealment adequate?						
978. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?						
979. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?						
980. Were groups similar at baseline?						
981. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?						
982. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?						
983. Was overall attrition less than 30%?						
984. Was differential attrition less than 15%?						
985. Does the analysis control for baseline						

differences between groups?						
986. Does the analysis account for differences in treatment received by the groups?						
987. Are the statistical methods used to assess the outcomes appropriate?						
988. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?						
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (___)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?	x						
Was a case-control design avoided?	x						
Did the study avoid inappropriate exclusions?	x						
Could the selection of patients have introduced bias?					x		
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?			x				
If a threshold was used, was it pre-specified?				x			
Could the conduct or interpretation of the index test have introduced bias?					x		
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?	x						
Were the reference standard results interpreted without knowledge of the results of the index test?			x				
Could the reference standard, its conduct, or its interpretation have introduced bias?					x		
Domain 4: Flow and Timing							
Did all patients receive a reference standard?	x						
Did patients receive the same reference standard?	x						
Were all patients included in the analysis?	x						
Could the patient flow have introduced bias?					x		
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
113	Nuyten	2008

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
989. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
990. For RCTs, were randomization and allocation concealment adequate?					X	
991. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
992. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?			X			odd comparison of the test of interest (MammaPrint) to an alternative gene signature
993. Were groups similar at baseline?						
994. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?						
995. Were outcomes assessed using valid and reliable measures, implemented consistently						

across all study participants?						
996. Was overall attrition less than 30%?				X		
997. Was differential attrition less than 15%?				X		
998. Does the analysis control for baseline differences between groups?	X					
999. Does the analysis account for differences in treatment received by the groups?	X					
1000. Are the statistical methods used to assess the outcomes appropriate?	X					
1001. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments: biggest concern about this study is that another gene signature with prognostic value and likely overlapping genetic info was included as a covariate, and this alternate signature is not a standard prognostic marker, skewing the analysis toward non-significance for the test of interest						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (___)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
1033	Ogino	2009

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1002. What is the study design?			**X**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1003. For RCTs, were randomization and allocation concealment adequate?					X	
1004. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
1005. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
1006. Were groups similar at baseline?			X			Similar for most characteristics; some small differences for MSI status and treatment arm
1007. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		

1008. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		Just report how DFS, RFS, OS were defined, but don't report information on how outcomes were ascertained
1009. Was overall attrition less than 30%?	X					
1010. Was differential attrition less than 15%?	X					
1011. Does the analysis control for baseline differences between groups?	X					
1012. Does the analysis account for differences in treatment received by the groups?	X					
1013. Are the statistical methods used to assess the outcomes appropriate?	X					
1014. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments: they created cohort from among subjects enrolled in an RCT comparing adjuvant chemotherapies for stage III CRC. This was 508 of the 1264 (those with tumor tissue available for KRAS sequencing). Article does nice job of exploring and addressing potential confounding through multivariate adjustment, stratification, and other statistical analyses. Group enrolled in this study were similar to the 700+ subjects that were in the RCT but not in this trial. Some risk of measurement bias as details are not reported for ascertainment.						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
1043	Ogino	2012

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1015. What is the study design?			**X**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1016. For RCTs, were randomization and allocation concealment adequate?					X	
1017. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
1018. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
1019. Were groups similar at baseline?		X				For BRAF mutation vs. wild-type, differences for sex, age, tumor location, MSI status, and KRAS
1020. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		

1021. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		
1022. Was overall attrition less than 30%?	X					
1023. Was differential attrition less than 15%?	X					
1024. Does the analysis control for baseline differences between groups?	X					
1025. Does the analysis account for differences in treatment received by the groups?	X					
1026. Are the statistical methods used to assess the outcomes appropriate?	X					
1027. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments: they created cohort from among subjects enrolled in an RCT comparing adjuvant chemotherapies for stage III CRC. This was 506 of the 1264 (those with tumor tissue available). Article does nice job of exploring and addressing potential confounding through multivariate adjustment, stratification, and other statistical analyses. Group enrolled in this study were similar to the 700+ subjects that were in the RCT but not in this trial. Some risk of measurement bias as details are not reported for ascertainment. For overall survival, the only outcome that remained statistically significantly different between BRAF mutation vs. wild-type, the risk of bias may be higher than for other outcomes because they did not adjust for many potential confounders that would influence overall survival.						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
1071	Pai	2012

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium		High	X	N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:	High risk of selection bias, confounding, attrition bias, and measurement bias. See comments box below for details.							

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (__)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1028. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1029. For RCTs, were randomization and allocation concealment adequate?					X	
1030. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
1031. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
1032. Were groups similar at baseline?		X				
1033. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?		X				
1034. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?		X				
1035. Was overall attrition less than 30%?				X		
1036. Was differential attrition less than 15%?				X		

1037. Does the analysis control for baseline differences between groups?			X			
1038. Does the analysis account for differences in treatment received by the groups?		X				
1039. Are the statistical methods used to assess the outcomes appropriate?			X			
1040. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?		X				
Comments: High risk of selection bias and confounding. The multivariate analysis only adjusted for stage. It did not consider sex, age, grade, cellular subtype (e.g. signet ring histology), or lymphovascular invasion. The baseline characteristics show potentially important differences for sex, lymph invasion, lymph node metastases, histology. Very little description of methods of assessing outcomes (DFS and OS) in this retrospective cohort. No reporting of masking of outcome assessors to genotypes. High risk of attrition bias as they do not report numbers lost to follow up clearly for the 3 different groups. For the OS analyses, lost to followup was treated the same as death. Not clear how missing data was handled for the DFS analysis.						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3276	Paik	2004

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1041. What is the study design?			**X**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1042. For RCTs, were randomization and allocation concealment adequate?					X	
1043. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?				X		
1044. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
1045. Were groups similar at baseline?				X		
1046. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
1047. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		Unclear ascertainment methods
1048. Was overall attrition less than 30%?				X		
1049. Was differential attrition less than 15%?				X		
1050. Does the analysis control for baseline				X		Data NR

differences between groups?						
1051. Does the analysis account for differences in treatment received by the groups?		X				
1052. Are the statistical methods used to assess the outcomes appropriate?	X					
1053. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?			X			
Comments: Concern for selection bias, measurement bias, and confounding, but insufficient reporting of Methods, subject characteristics, and Results to adequately determine risk of bias.						

Key Question 2					If study does NOT apply to this KQ, place an 'X' here (___)		
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
1081	Pang	2011

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High	X	N/A	
Risk of bias for KQ 3:	Low		Medium		High		N/A	X
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:	See comments below. This article isn't really designed to answer our questions of interest. I see why we may have included it (although it would be reasonable to exclude it for wrong comparison because it is mainly about comparing results of testing metastases with results of the primary tumor) because there is a small detail that we could mention, but for our questions, this has a high risk of bias given the design and selection.							

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (_X_)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1054. What is the study design?						
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1055. For RCTs, were randomization and allocation concealment adequate?						
1056. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?						
1057. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?						
1058. Were groups similar at baseline?						
1059. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?						
1060. Were outcomes assessed using valid and reliable measures, implemented consistently						

across all study participants?						
1061. Was overall attrition less than 30%?						
1062. Was differential attrition less than 15%?						
1063. Does the analysis control for baseline differences between groups?						
1064. Does the analysis account for differences in treatment received by the groups?						
1065. Are the statistical methods used to assess the outcomes appropriate?						
1066. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?						
Comments:						

Key Question 2					If study does NOT apply to this KQ, place an 'X' here (___)		
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?		X					
Was a case-control design avoided?	X						
Did the study avoid inappropriate exclusions?			X				
Could the selection of patients have introduced bias?						X	
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?				X			
If a threshold was used, was it pre-specified?				X			
Could the conduct or interpretation of the index test have introduced bias?					X		
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?	X						
Were the reference standard results interpreted without knowledge of the results of the index test?			X				
Could the reference standard, its conduct, or its interpretation have introduced bias?					X		
Domain 4: Flow and Timing							
Did all patients receive a reference standard?	X						
Did patients receive the same reference standard?	X						
Were all patients included in the analysis?		X					
Could the patient flow have introduced bias?						X	
Comments: High risk of bias for our questions, with just 11 cases chosen by an unclear method. It's hard to find any relevant, useful information in this article for the questions that we're asking. If we were interested in how similar the results from testing of metastases are to results of testing primary tumors, this would possibly be more useful. Note: Many of the risk of bias questions are not relevant for this particular article because it is not looking at a test of interest compared with a gold standard. It just contributes a very small piece of potentially relevant data about how many samples returned a valid result (8 of 11) and about tissue acceptance criteria (which was something that was predetermined in their methods, not something determined by the results of the study).							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
1683	Phipps	2012

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1067. What is the study design?			**X**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1068. For RCTs, were randomization and allocation concealment adequate?					X	
1069. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
1070. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
1071. Were groups similar at baseline?		X				Differences for age, sex, tumor site, stage, MSI status
1072. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
1073. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	X					SEER and National Death Index

1074. Was overall attrition less than 30%?	X					
1075. Was differential attrition less than 15%?				X		Of the 27% without BRAF status, no information available to determine differential attrition
1076. Does the analysis control for baseline differences between groups?	X					
1077. Does the analysis account for differences in treatment received by the groups?		X				They did not have treatment information and did not adjust for differences in treatment
1078. Are the statistical methods used to assess the outcomes appropriate?	X					
1079. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments: Moderate potential risk of survivor bias; BRAF mutation status was not determined in 27% of enrolled cases, nor was it determined in cases who were eligible for the study but were not enrolled; analyses were based on the 1980/2708 with BRAF results determined; analyses did not account for differences in treatment						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3417	Poulet	2012

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low	*	Medium	*	High	*	N/A	
Risk of bias for KQ 3:	Low		Medium		High		N/A	X
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:	unclear							

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (_X_)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1080. What is the study design?						
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1081. For RCTs, were randomization and allocation concealment adequate?						
1082. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?						
1083. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?						
1084. Were groups similar at baseline?						
1085. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?						
1086. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?						
1087. Was overall attrition less than 30%?						
1088. Was differential attrition less than 15%?						
1089. Does the analysis control for baseline						

differences between groups?						
1090. Does the analysis account for differences in treatment received by the groups?						
1091. Are the statistical methods used to assess the outcomes appropriate?						
1092. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?						
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (___)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?			X				
Was a case-control design avoided?	X						
Did the study avoid inappropriate exclusions?			X				
Could the selection of patients have introduced bias?							X
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?	X						
If a threshold was used, was it pre-specified?			X				
Could the conduct or interpretation of the index test have introduced bias?					X		
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?				X			
Were the reference standard results interpreted without knowledge of the results of the index test?				X			
Could the reference standard, its conduct, or its interpretation have introduced bias?					NA	NA	NA
Domain 4: Flow and Timing							
Did all patients receive a reference standard?				X			
Did patients receive the same reference standard?				X			
Were all patients included in the analysis?	X						
Could the patient flow have introduced bias?					X		
Comments: No reference standard in this because it's just reporting how many times a valid result was returned for Mammaprint and for Oncotype Dx, and comparing that, as well as how many times they both got low, intermed, or high risk on the same samples.							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
161	Rayhanabad	2012

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium		High		N/A	X
Risk of bias for KQ 4a:	Low	x	Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1093. What is the study design?						**X**
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1094. For RCTs, were randomization and allocation concealment adequate?					X	
1095. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
1096. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?					X	
1097. Were groups similar at baseline?					X	
1098. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?					X	
1099. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	X					
1100. Was overall attrition less than 30%?					X	
1101. Was differential attrition less than 15%?					X	
1102. Does the analysis control for baseline					X	

differences between groups?						
1103. Does the analysis account for differences in treatment received by the groups?					X	
1104. Are the statistical methods used to assess the outcomes appropriate?	X					
1105. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?						
Comments: Altho retrospective decision of change in management is based on comparing the NCCN guidelines so do not think there is a risk of bias						

Key Question 2				If study does NOT apply to this KQ, place an 'X' here (_X_)			
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
1194	Roth	2010

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1106. What is the study design?			**X**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1107. For RCTs, were randomization and allocation concealment adequate?					X	
1108. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
1109. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
1110. Were groups similar at baseline?				X		
1111. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
1112. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	X					
1113. Was overall attrition less than 30%?	X					
1114. Was differential attrition less than 15%?	X					
1115. Does the analysis control for baseline				X		

differences between groups?						
1116. Does the analysis account for differences in treatment received by the groups?	X					
1117. Are the statistical methods used to assess the outcomes appropriate?	X					
1118. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					

Comments: Unable to determine baseline comparison for the comparison we're interested in (BRAF mutation vs. wild-type and KRAS mutation vs. wildtype); Study reports baseline data for 3 groups (all subjects, stage II, and stage III). Can't determine if analysis controls for baseline differences between groups, but it does control for many variables, including most known prognostic factors.

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3649	Roth	2012

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1119. What is the study design?			**X**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1120. For RCTs, were randomization and allocation concealment adequate?					X	
1121. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
1122. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
1123. Were groups similar at baseline?				X		
1124. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
1125. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		
1126. Was overall attrition less than 30%?				X		
1127. Was differential attrition less than 15%?				X		
1128. Does the analysis control for baseline				X		

differences between groups?						
1129. Does the analysis account for differences in treatment received by the groups?	X					
1130. Are the statistical methods used to assess the outcomes appropriate?	X					
1131. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments:						

Key Question 2					If study does NOT apply to this KQ, place an 'X' here (_X_)		
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
2992	Rouquette	2012

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low	X	Medium		High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1132. What is the study design?			**x**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1133. For RCTs, were randomization and allocation concealment adequate?					x	
1134. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	x					
1135. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	x					
1136. Were groups similar at baseline?				x		
1137. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?					x	death is outcome blinding unlikely to matter
1138. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	x					
1139. Was overall attrition less than 30%?				x		
1140. Was differential attrition less than 15%?				x		

1141. Does the analysis control for baseline differences between groups?				x		
1142. Does the analysis account for differences in treatment received by the groups?	x					
1143. Are the statistical methods used to assess the outcomes appropriate?	x					
1144. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	x					
Comments: survival analysis was not the primary focus of the study and risk ratios were not presented, so very difficult to determine if sample size or other factors were drivers of non-significant findings						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3986	Saghatchian	2012

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High				N/A	X
Risk of bias for KQ 2:	Low		Medium		High				N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High				N/A	
Risk of bias for KQ 4a:	Low		Medium		High				N/A	X
Risk of bias for KQ 4b:	Low		Medium		High				N/A	X
Risk of bias for KQ 5:	Low		Medium		High				N/A	X
Explain any **High** ratings:										

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1145. What is the study design?			**X**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1146. For RCTs, were randomization and allocation concealment adequate?					X	
1147. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
1148. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
1149. Were groups similar at baseline?		X				Many differences (Table 1)
1150. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
1151. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		Outcomes were related to death, metastases, and recurrence

						measures. No description of ascertainment methods
1152. Was overall attrition less than 30%?				X		
1153. Was differential attrition less than 15%?				X		
1154. Does the analysis control for baseline differences between groups?	X					
1155. Does the analysis account for differences in treatment received by the groups?		X				
1156. Are the statistical methods used to assess the outcomes appropriate?	X					
1157. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3652	Samadder	2013

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1158. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1159. For RCTs, were randomization and allocation concealment adequate?					X	
1160. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
1161. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
1162. Were groups similar at baseline?				X		
1163. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
1164. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	X					
1165. Was overall attrition less than 30%?	X					
1166. Was differential attrition less than 15%?				X		
1167. Does the analysis control for baseline				X		

differences between groups?						
1168. Does the analysis account for differences in treatment received by the groups?	X					Adjusted for chemo exposure and radiation exposure
1169. Are the statistical methods used to assess the outcomes appropriate?	X					
1170. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
1226	Samowitz	2005

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium		High	X	N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:	High risk of selection bias and confounding. See comments below.							

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1171. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1172. For RCTs, were randomization and allocation concealment adequate?					X	
1173. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
1174. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
1175. Were groups similar at baseline?		X				
1176. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
1177. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	X					
1178. Was overall attrition less than 30%?				X		
1179. Was differential attrition less than 15%?				X		
1180. Does the analysis control for baseline			X			

differences between groups?						
1181. Does the analysis account for differences in treatment received by the groups?		X				
1182. Are the statistical methods used to assess the outcomes appropriate?	X					
1183. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?		X				
Comments: Analysis adjusted for age, stage, tumor site, and CIMP; did not consider other prognostic factors, such as grade, cellular subtypes, LV invasion, location (rectum vs. colon), sex, margin status—and there were significant baseline differences between the groups for some of these factors (tumor site, differentiation, mucinous histology). High risk of selection bias and confounding given the baseline differences and many factors not included in the multivariate analysis.						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3514	Schneider	2012

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium		High		N/A	X
Risk of bias for KQ 4a:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1184. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1185. For RCTs, were randomization and allocation concealment adequate?					X	
1186. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
1187. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
1188. Were groups similar at baseline?		X				Differences for grade and AOL
1189. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
1190. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		
1191. Was overall attrition less than 30%?	X					

1192. Was differential attrition less than 15%?	X					
1193. Does the analysis control for baseline differences between groups?		X				
1194. Does the analysis account for differences in treatment received by the groups?	X					
1195. Are the statistical methods used to assess the outcomes appropriate?	X					
1196. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?					X	
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3012	Scoccianti	

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1197. What is the study design?			**x**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1198. For RCTs, were randomization and allocation concealment adequate?					x	
1199. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	x					
1200. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	x					
1201. Were groups similar at baseline?		x				non-randomized study
1202. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?					x	outcome is survival
1203. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	x					
1204. Was overall attrition less than 30%?	x					

1205. Was differential attrition less than 15%?					x	
1206. Does the analysis control for baseline differences between groups?			x			
1207. Does the analysis account for differences in treatment received by the groups?		x				
1208. Are the statistical methods used to assess the outcomes appropriate?	x					
1209. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	x					
Comments: most standard prognostic markers were used in multivariable analysis (T and N size) however only covariates with significant univariate associations were included in the multivariable model, iffy way of reducing a model						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
1264	Shaukat	2010

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1210. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1211. For RCTs, were randomization and allocation concealment adequate?					X	
1212. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
1213. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
1214. Were groups similar at baseline?				X		analysis was cohort nested in a case-control, full demographics not presented by cohort groups
1215. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?					X	

1216. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	X					
1217. Was overall attrition less than 30%?				X		
1218. Was differential attrition less than 15%?				X		
1219. Does the analysis control for baseline differences between groups?			X			adjusted analysis is presented but since baseline comparison between groups not presented, unable to assess if fully adjusted
1220. Does the analysis account for differences in treatment received by the groups?		X				
1221. Are the statistical methods used to assess the outcomes appropriate?	X					
1222. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?			X			
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (___)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
1272	Shia	2008

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium		High	X	N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:	High risk of selection bias, attrition bias, measurement bias, and confounding. See comments below for additional details.							

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (__)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1223. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1224. For RCTs, were randomization and allocation concealment adequate?					X	
1225. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
1226. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
1227. Were groups similar at baseline?				X		For our comparison of interest (by MSI status), no information reported
1228. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
1229. Were outcomes assessed using valid and				X		Used a surgical

reliable measures, implemented consistently across all study participants?						database to gather clinical information and outcomes; no further information reported on ascertainment, definitions of outcomes, masking of outcome assessors
1230. Was overall attrition less than 30%?		X				Of 236 patients included, complete clinical information available for only 130 (55%) and MSI detection completed in just 77 (32.6%)
1231. Was differential attrition less than 15%?				X		
1232. Does the analysis control for baseline differences between groups?				X		
1233. Does the analysis account for differences in treatment received by the groups?		X				
1234. Are the statistical methods used to assess the outcomes appropriate?	X					
1235. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?				X		
Comments: High risk of selection bias, attrition bias, measurement bias, and confounding. Just 32.6% of the sample had MSI results and just 55% of the sample had complete clinical information. Because the article is focused on FR alpha, it reports little information about the MSI results and analyses. The multivariate model is not reported, nor are the outcomes data for MSI from the multivariate model. It just tells us that only TNM staging remained significant predictor for DSS in the multivariate analysis (Cox regression with forward selection, which was limited to 3 covariated due to the limited number of events).						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							

Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3348	Solin	2012

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1236. What is the study design?			**X**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1237. For RCTs, were randomization and allocation concealment adequate?					X	
1238. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
1239. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
1240. Were groups similar at baseline?					X	
1241. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?	X					
1242. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	X					
1243. Was overall attrition less than 30%?	X					
1244. Was differential attrition less than 15%?	X					
1245. Does the analysis control for baseline					X	

differences between groups?						
1246. Does the analysis account for differences in treatment received by the groups?					X	
1247. Are the statistical methods used to assess the outcomes appropriate?			X – Since there were differences by ER positive and negative. Should have stratified or used an interaction term			
1248. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?						
Comments:						

Key Question 2	X						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
1311	Soreide	2009

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1249. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1250. For RCTs, were randomization and allocation concealment adequate?					X	
1251. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
1252. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
1253. Were groups similar at baseline?		X				Differences for site, size, LN status, grade, ploidy, stage
1254. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
1255. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		Unclear how outcomes were assessed. No

						reporting of followup plans/schedule; only reports that recurrence was recorded during follow up and was defined as any locoregional recurrence, distant metastases, or both; no description of how recurrence was determined
1256. Was overall attrition less than 30%?	X					
1257. Was differential attrition less than 15%?	X					
1258. Does the analysis control for baseline differences between groups?	X					
1259. Does the analysis account for differences in treatment received by the groups?		X				But the methods suggests that there was little variation in treatment
1260. Are the statistical methods used to assess the outcomes appropriate?	X					
1261. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments: Unclear if this was prospective or retrospective; it sounds like some information was collected retrospectively; difficult to assess risk of ascertainment bias as very little information reported; no attempt to consider differences in treatment						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							

Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
2558	Sriram	2011

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low	x	Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium		High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (_x_)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1262. What is the study design?						
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1263. For RCTs, were randomization and allocation concealment adequate?						
1264. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?						
1265. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?						
1266. Were groups similar at baseline?						
1267. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?						
1268. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?						
1269. Was overall attrition less than 30%?						
1270. Was differential attrition less than 15%?						
1271. Does the analysis control for baseline						

differences between groups?							
1272. Does the analysis account for differences in treatment received by the groups?							
1273. Are the statistical methods used to assess the outcomes appropriate?							
1274. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?							
Comments:							

Key Question 2					If study does NOT apply to this KQ, place an 'X' here (___)		
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?			x				
Was a case-control design avoided?	x						
Did the study avoid inappropriate exclusions?	x						
Could the selection of patients have introduced bias?					x		
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?			x				
If a threshold was used, was it pre-specified?	x						
Could the conduct or interpretation of the index test have introduced bias?					x		
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?	x						
Were the reference standard results interpreted without knowledge of the results of the index test?			x				
Could the reference standard, its conduct, or its interpretation have introduced bias?					x		
Domain 4: Flow and Timing							
Did all patients receive a reference standard?	x						
Did patients receive the same reference standard?	x						
Were all patients included in the analysis?							
Could the patient flow have introduced bias?					x		
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3432	Srivastava	2013

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium		High		N/A	X
Risk of bias for KQ 4a:	Low		Medium		High	Unclear	N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

1275. What is the study design?	**RCT**	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
		Uncontrolled trial				
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1276. For RCTs, were randomization and allocation concealment adequate?					X	
1277. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?				X		
1278. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
1279. Were groups similar at baseline?					X	
1280. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
1281. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		
1282. Was overall attrition less than 30%?				X		

1283. Was differential attrition less than 15%?				X		
1284. Does the analysis control for baseline differences between groups?					X	
1285. Does the analysis account for differences in treatment received by the groups?					X	
1286. Are the statistical methods used to assess the outcomes appropriate?				X		
1287. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?					X	
Comments: Unclear risk of bias; very limited reporting of methods in this abstract from a conference; all physicians were from 1 site; unclear methods of ascertainment; unclear selection bias and measurement bias						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
124	Tang	2011

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low	X	Medium		High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1288. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1289. For RCTs, were randomization and allocation concealment adequate?					X	
1290. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
1291. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
1292. Were groups similar at baseline?	X					
1293. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?					X	
1294. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	X					
1295. Was overall attrition less than 30%?				X		
1296. Was differential attrition less than 15%?				X		
1297. Does the analysis control for baseline	X					

differences between groups?						
1298. Does the analysis account for differences in treatment received by the groups?		X				patients all treated similarly
1299. Are the statistical methods used to assess the outcomes appropriate?	X					
1300. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (X__)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
1373	Tie	2010

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1301. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1302. For RCTs, were randomization and allocation concealment adequate?					X	
1303. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?				X		Unclear how they selected the 600 cases from the 1674 in the database
1304. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
1305. Were groups similar at baseline?		X				
1306. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
1307. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		Details of methods of ascertaining outcomes NR; we know they

						used a database (BioGrid Austrialia), but no information about validity of that database is provided, or about how they determined recurrence, etc. to input into the database
1308. Was overall attrition less than 30%?	X					
1309. Was differential attrition less than 15%?	X					
1310. Does the analysis control for baseline differences between groups?			X			Did for age, site, stage, but did not adjust for gender
1311. Does the analysis account for differences in treatment received by the groups?	X					
1312. Are the statistical methods used to assess the outcomes appropriate?	X					
1313. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					Adjusted for age, stage, site, adjuvant treatment; did not adjust for grade, cellular subtypes, sex, lymphovascular invasion
Comments: Follow up was perhaps too short to collect good outcomes data on recurrence and mortality (median 38.5 months for stage I to III patients)						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic							

markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3057	Tsao	2011

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low	x	Medium		High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1314. What is the study design?			**x**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1315. For RCTs, were randomization and allocation concealment adequate?					x	
1316. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	x					
1317. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	x					
1318. Were groups similar at baseline?		x				Not expected in non-randomized trial
1319. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?		x				Outcome is survival
1320. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	X					
1321. Was overall attrition less than 30%?				X		

1322. Was differential attrition less than 15%?				X		
1323. Does the analysis control for baseline differences between groups?	X					
1324. Does the analysis account for differences in treatment received by the groups?			x			Controls for type of resection, on a clinical trial so distribution of chemo should be similar between groups
1325. Are the statistical methods used to assess the outcomes appropriate?	x					
1326. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	x					
Comments:						

Key Question 2					If study does NOT apply to this KQ, place an 'X' here (___)		
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3332	Van de Vijver	2002

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low	X	Medium		High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1327. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1328. For RCTs, were randomization and allocation concealment adequate?					X	
1329. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
1330. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
1331. Were groups similar at baseline?		X				
1332. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?					X	
1333. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	X					
1334. Was overall attrition less than 30%?				X		
1335. Was differential attrition less than 15%?				X		
1336. Does the analysis control for baseline	X					

differences between groups?						
1337. Does the analysis account for differences in treatment received by the groups?	X					
1338. Are the statistical methods used to assess the outcomes appropriate?	X					
1339. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments:						

Key Question 2					If study does NOT apply to this KQ, place an 'X' here (___)		
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3333	Van't Veer	2002

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium	X	High		N/A	
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

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KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1340. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1341. For RCTs, were randomization and allocation concealment adequate?					X	
1342. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
1343. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
1344. Were groups similar at baseline?				X		
1345. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?					X	
1346. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		
1347. Was overall attrition less than 30%?				X		
1348. Was differential attrition less than 15%?				X		
1349. Does the analysis control for baseline				X		

differences between groups?						
1350. Does the analysis account for differences in treatment received by the groups?				X		
1351. Are the statistical methods used to assess the outcomes appropriate?	X					
1352. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments: only one paragraph in short article describes multivariate analysis, many details not shown						

Key Question 2					If study does NOT apply to this KQ, place an 'X' here (___)		
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?			X				
Was a case-control design avoided?		X					
Did the study avoid inappropriate exclusions?		X					
Could the selection of patients have introduced bias?						X	
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?				X			
If a threshold was used, was it pre-specified?		X					
Could the conduct or interpretation of the index test have introduced bias?							X
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?	X						
Were the reference standard results interpreted without knowledge of the results of the index test?	X						
Could the reference standard, its conduct, or its interpretation have introduced bias?					X		
Domain 4: Flow and Timing							
Did all patients receive a reference standard?	X						
Did patients receive the same reference standard?	X						
Were all patients included in the analysis?	X						
Could the patient flow have introduced bias?					X		
Comments: Reference standard was ascertainment of actual outcome from medical records, test was not compared to another prognostic test. Patients were selected based on whether they had metastases or not case-control) and article does not state whether they were randomly, consecutively or otherwise selected. All patients were <55 years old and reason for this exclusion is not stated.							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
3354	Venook	2013

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1353. What is the study design?			**X**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1354. For RCTs, were randomization and allocation concealment adequate?					X	
1355. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
1356. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
1357. Were groups similar at baseline?				X		
1358. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
1359. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	X					
1360. Was overall attrition less than 30%?	X					
1361. Was differential attrition less than 15%?	X					
1362. Does the analysis control for baseline				X		

differences between groups?						
1363. Does the analysis account for differences in treatment received by the groups?				X		
1364. Are the statistical methods used to assess the outcomes appropriate?	X					
1365. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (___)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
43	Whitson	2009

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low	x	Medium		High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1366. What is the study design?			**x**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1367. For RCTs, were randomization and allocation concealment adequate?					x	
1368. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	x					
1369. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	x					
1370. Were groups similar at baseline?		x				non-randomized
1371. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				x		outcome was survival
1372. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	x					
1373. Was overall attrition less than 30%?				x		
1374. Was differential attrition less than 15%?				x		

1375. Does the analysis control for baseline differences between groups?	x					
1376. Does the analysis account for differences in treatment received by the groups?					x	all treated similarly
1377. Are the statistical methods used to assess the outcomes appropriate?	x					
1378. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	x					
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (___)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
2684	Woo	2009

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (__)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1379. What is the study design?			**X**			
If "Other" study design, enter a description in this box: Uncontrolled trial	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1380. For RCTs, were randomization and allocation concealment adequate?					X	
1381. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
1382. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
1383. Were groups similar at baseline?		X				
1384. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
1385. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	X					
1386. Was overall attrition less than 30%?				X		
1387. Was differential attrition less than 15%?				X		

1388. Does the analysis control for baseline differences between groups?		X				
1389. Does the analysis account for differences in treatment received by the groups?					X	
1390. Are the statistical methods used to assess the outcomes appropriate?	X					
1391. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments:						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (___)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
4004	Yamauchi	2013

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium		High		N/A	X
Risk of bias for KQ 4a:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1392. What is the study design?			**X**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1393. For RCTs, were randomization and allocation concealment adequate?					X	
1394. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					Consecutive sample was offered entry, To participate in the study, patients were required to incur the costs of the assay as an out-of-pocket expense
1395. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
1396. Were groups similar at baseline?				X		Not reported by test result
1397. Were the outcome assessors blinded to				X		But, not as important as

the test result/intervention/exposure status of participants?						some studies since the outcome is the questionnaire result
1398. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		Modified a published questionnaire; no information provided on the validity and reliability
1399. Was overall attrition less than 30%?	X					
1400. Was differential attrition less than 15%?	X					
1401. Does the analysis control for baseline differences between groups?		X				
1402. Does the analysis account for differences in treatment received by the groups?					X	
1403. Are the statistical methods used to assess the outcomes appropriate?			X			Some concern for stopping enrollment early, and their justification for doing so. See comments below
1404. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?					X	
Comments: The study was designed to enroll 200 patients, with the original intent to estimate a decision change rate of 20% with a precision of `5% to 6%. However, it was decided to halt enrollment after 124 patients were enrolled because the accumulating data indicated that there were statistically significant reductions in treatment recommendations for chemotherapy in N0 and Nþ patient subgroups.						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have							

introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
1516	Yoon	2011

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low	X	Medium		High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1405. What is the study design?			**X**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1406. For RCTs, were randomization and allocation concealment adequate?					X	
1407. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
1408. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
1409. Were groups similar at baseline?		X				Differences for age, site, size, LN metastases, histology and synchronous adenomas
1410. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?				X		
1411. Were outcomes assessed using valid and	X					

reliable measures, implemented consistently across all study participants?						
1412. Was overall attrition less than 30%?	X					
1413. Was differential attrition less than 15%?	X					
1414. Does the analysis control for baseline differences between groups?	X					
1415. Does the analysis account for differences in treatment received by the groups?			X			Accounts for differences in adjuvant chemo, but not differences in radiation (among the 770 with rectal cancer, 41% got postop radiation); however, not too concerning because 97% of the rectal cancer cases were MSS and analyses found MSI-H to have better outcomes
1416. Are the statistical methods used to assess the outcomes appropriate?	X					
1417. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					Table 3
Comments: age, sex, location, CEA, growth type, LN metastasis, distant metastasis, lymphovascular invasion, histology, and adjuvant chemotherapy included in the multivariate analysis in Table 3 for DFS and OS.						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (_X_)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							

Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
162	Yorozuya	2009

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	
Risk of bias for KQ 2:	Low		Medium		High		N/A	
Risk of bias for KQ 3:	Low		Medium	x	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	
Risk of bias for KQ 4b:	Low		Medium		High		N/A	
Risk of bias for KQ 5:	Low		Medium		High		N/A	
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)
KQ 1: Overarching Question Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?	
KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?	
KQ 4a. Clinical Utility. What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?	
KQ 4b. Clinical Utility. What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?	
KQ 5. Harms. What are the harms associated with treatment decisions that are informed by the genetic tests?	

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1418. What is the study design?					**x**	
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1419. For RCTs, were randomization and allocation concealment adequate?					x	
1420. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	x					
1421. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	x					
1422. Were groups similar at baseline?			x			matched on age but some differences bet cases and controls on clinical covariates
1423. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?		x				
1424. Were outcomes assessed using valid and				x		assuming outcome of

reliable measures, implemented consistently across all study participants?						metastatic disease was determined by chart review, but not stated
1425. Was overall attrition less than 30%?					x	
1426. Was differential attrition less than 15%?					x	
1427. Does the analysis control for baseline differences between groups?	x					
1428. Does the analysis account for differences in treatment received by the groups?		x				does not control although cases and controls were similar in this respect
1429. Are the statistical methods used to assess the outcomes appropriate?	x					
1430. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?						
Comments:						

Key Question 2					If study does NOT apply to this KQ, place an 'X' here (_X_)		
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
67	Zellweger	2006

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium		High	X	N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:	See comments below in comments box							

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1431. What is the study design?			**X**			
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1432. For RCTs, were randomization and allocation concealment adequate?					X	
1433. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?				X		
1434. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
1435. Were groups similar at baseline?				X		
1436. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?		X				
1437. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				X		
1438. Was overall attrition less than 30%?				X		
1439. Was differential attrition less than 15%?				X		
1440. Does the analysis control for baseline				X		

differences between groups?						
1441. Does the analysis account for differences in treatment received by the groups?		X				
1442. Are the statistical methods used to assess the outcomes appropriate?			X			
1443. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?				X		

Comments: High risk of selection bias as the article does not report inclusion/exclusion criteria, method of selecting the 138 subjects (e.g. was it consecutive? Random? Other?), or comparison of groups at baseline. There is no information provided that allows us to determine how similar/different the FISH + vs. FISH – groups were at baseline. Also, no information about attrition provided: of the 138, median follow up was 19 months (range 4 - 52), but no data reported about how many were lost early in the study and whether it was differential for the FISH + vs. FISH – groups. High risk of measurement bias as they don't give any information about how recurrence was determined and they don't describe any masking of outcome assessors. Although it's hard to assess their multivariate analysis because they don't report what they adjusted for in the Cox model, I would probably consider the analysis to have a high risk of confounding because they don't describe adjustment for known prognostic factors (e.g., stage, presence of CIS). In addition, since we don't have information on how demographics or potential confounders were distributed at baseline, we can't even assess what else they should have adjusted for.

Key Question 2

If study does NOT apply to this KQ, place an 'X' here (_X_)

KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?

	Yes	No	Unclear	NA	Low	High	Unclear
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							

Comments:

Worksheet for Risk of Bias of Individual Studies – GTRRC (v. 4-23-13)

Ref ID #	Author	Year
1533	Zlobec	2009

Indicate the appropriate risk of bias rating by placing an 'X' in the shaded space to the right of the rating for each KQ that is applicable. If a study does not apply to a KQ, put an 'X' next to N/A.

Risk of bias for KQ 1:	Low		Medium		High		N/A	X
Risk of bias for KQ 2:	Low		Medium		High		N/A	X
Risk of bias for KQ 3:	Low		Medium	X	High		N/A	
Risk of bias for KQ 4a:	Low		Medium		High		N/A	X
Risk of bias for KQ 4b:	Low		Medium		High		N/A	X
Risk of bias for KQ 5:	Low		Medium		High		N/A	X
Explain any **High** ratings:								

Low: Study has minimal bias. High degree of confidence that the true effect size is similar in size and direction to that reported.
Medium: Study has at least one significant source of bias, but does not have flaws that are likely to cause major bias. Moderate degree of confidence that the actual effect is in the direction reported by the study; moderate degree of confidence that the true effect size is similar to that reported.
High: Study has at least one major sources of bias or multiple significant sources of bias. Low degree of confidence that the true effect size is similar in size or direction to that reported.
NA: Not applicable to that key question.

Key Questions 1, 3, 4a, 4b, and 5	If the study does NOT apply to any of these KQs, place an 'X' here (___)

KQ 1: Overarching Question
Is there direct evidence that the addition of the following genetic tests used alone or in combination with traditional prognostic factors change physician decision making and improve outcomes for adult patients with lung, breast, colorectal, and bladder cancer compared with the use of traditional factors to predict risk of recurrence for adults with these cancers?

KQ 3. Clinical Validity. Does existing evidence establish the prognostic accuracy of the tests for predicting recurrence?

KQ 4a. Clinical Utility.
What is the evidence that the prognostic information provided by the genetic tests modifies physician decisions regarding use of adjuvant anti-neoplastic chemo- and/or radiotherapy; enhanced diagnostic testing for recurrence; and/or preventive surgery among adult patients with malignant tumors?

KQ 4b. Clinical Utility.
What is the evidence that modified decisions lead to improved overall survival, disease free survival, time to recurrence, quality of life, or incidence of serious side effects of adjuvant therapy in adult patients with malignant tumors?

KQ 5. Harms.
What are the harms associated with treatment decisions that are informed by the genetic tests?

	RCT	**non-RCT**	**Prospective cohort study**	**Retrospective cohort study**	**Case-control study**	**Case Series**
1444. What is the study design?				**X**		
If "Other" study design, enter a description in this box:	**Yes**	**No**	**Partially**	**Can't Determine**	**NA**	**Explanation**
1445. For RCTs, were randomization and allocation concealment adequate?					X	
1446. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study?	X					
1447. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	X					
1448. Were groups similar at baseline?		X				
1449. Were the outcome assessors blinded to the test result/intervention/exposure status of participants?	X					
1450. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	X					
1451. Was overall attrition less than 30%?	X					
1452. Was differential attrition less than 15%?	X					
1453. Does the analysis control for baseline	X					

differences between groups?						
1454. Does the analysis account for differences in treatment received by the groups?		X				Tissues were from pre-operatively untreated patients. No information about treatment
1455. Are the statistical methods used to assess the outcomes appropriate?	X					
1456. **For KQ3 ONLY** – Did analyses adjust for all or most of the standard prognostic markers?	X					
Comments: Treatment & Distant metastasis information not available. Both factors affect CSS.						

Key Question 2	If study does NOT apply to this KQ, place an 'X' here (___)						
KQ 2. Analytic Validity. Does existing evidence establish the technical accuracy and reliability of the tests for detecting the relevant genetic markers?							
	Yes	**No**	**Unclear**	**NA**	**Low**	**High**	**Unclear**
Domain 1: Patient Selection							
Was a consecutive or random sample of patients enrolled?							
Was a case-control design avoided?							
Did the study avoid inappropriate exclusions?							
Could the selection of patients have introduced bias?							
Domain 2: Index Test(s)							
Were the index test results interpreted without knowledge of the results of the reference standard?							
If a threshold was used, was it pre-specified?							
Could the conduct or interpretation of the index test have introduced bias?							
Domain 3: Reference Standard							
Is the reference standard likely to correctly classify the genetic markers?							
Were the reference standard results interpreted without knowledge of the results of the index test?							
Could the reference standard, its conduct, or its interpretation have introduced bias?							
Domain 4: Flow and Timing							
Did all patients receive a reference standard?							
Did patients receive the same reference standard?							
Were all patients included in the analysis?							
Could the patient flow have introduced bias?							
Comments:							

Appendix D. Strength of Evidence (SOE)

Table D-1. EGFR for lung carcinoma

Outcome	Study Design: No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Other	Result/ Effect Size (CI)	Strength of Evidence
Risk of Recurrence	Cohort: 6 (1,870)	Medium	Indirect	Consistent	Imprecise	None	0.87(0.65,1.15) No Association[a]	Low
Cancer-specific mortality	None	NA	NA	NA	NA	NA	NA	NA
Overall survival	Cohort: 6 (1,820)	Medium	Indirect	Consistent	Imprecise	NA	0.77(0.5, 1.19) No Association[b]	Insufficient
Decisions about treatment								
Analytic Validity	5;898	Low	Direct	Consistent	Precise			High
Sensitivity and specificity	5;898	Low	Direct	Consistent	Precise			High
Positive and negative predictive value	5;898	Low	Direct	Consistent	Precise			High
Cross-lab validity	5;636	Low	Direct	Consistent	Precise	CAP Report Data		High

[a] Two studies did not report a hazard ratio for risk of recurrence, therefore 4 studies (N=936) contributed data to the meta-analysis.

[b] Two studies did not report a hazard ratio for overall survival, therefore 4 studies (N=834) contributed data to the meta-analysis.

Abbreviations: CI = confidence interval; N = number.

Table D-2. KRAS for lung carcinoma

Outcome	Study Design: No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Other	Result/ Effect Size (CI)	Strength of Evidence
Risk of Recurrence	Cohort: 4 (N=611)	Medium	Indirect	Inconsistent	Imprecise	None	2.84(1.14, 7.1)[a] KRAS mutation associated with greater RR	Insufficient
Cancer-specific mortality	None	NA	NA	NA	NA	NA	NA	NA
Overall survival	Cohort: 2 (N=253)	Medium	Indirect	Unknown (single study)	Unknown (single study)	None	OR, 2.69(1.91,3.80)) ; 3.33 (1.03, 10.82) mutation associated with lower OS	Insufficient
Decisions about treatment	0/0	NA	NA	NA	NA	NA	NA	NA
Analytic Validity	2;188	Low	Direct	Consistent	Precise			Moderate
Sensitivity and specificity	1;114	Low	Direct	Consistency Unknown (Single Study)	Precise			Low
Positive and negative predictive value	1;114	Low	Direct	Consistency Unknown (Single Study)	Precise			Low
Cross-lab validity	4;686	Low	Direct	Consistent	Precise	CAP Report Data		High

[a] Three studies representing 4 cohorts (N=611) contributed to the meta-analysis.

Abbreviations: CI = confidence interval; N = number.

Table D-3. Microsatellite instability for colorectal carcinoma

Outcome	Study Design: No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Other	Result/ Effect Size (CI)	Strength of Evidence
Risk of Recurrence	Cohort studies: 10 (7,130)	Medium	Indirect	Inconsistent	Imprecise	NA	MSI-H vs. MSS: HR, 0.60 (0.50 to 0.72) for the association between MSI status and recurrence	Insufficient
Cancer-specific mortality	Cohort studies: 6 (3,439)	Medium	Indirect	Inconsistent	Imprecise	NA	MSI-H vs. MSS: HR, 0.65 (0.51 to 0.82)[a] for the association between MSI status and cancer-specific mortality	Insufficient
Overall survival	Cohort studies: 12 (8,839)	Medium	Indirect	Inconsistent	Imprecise	NA	MSI-H vs. MSS: HR, 0.57 (0.43 to 0.77)[b] for the association between MSI status and OS;	Insufficient
Decisions about treatment	0 (0)	NA	NA	NA	NA	NA	NA	Insufficient
Analytic Validity	NA	NA	NA	NA	NA		NA	NA
Sensitivity and specificity	NA	NA	NA	NA	NA		NA	NA
Positive and negative predictive value	NA	NA	NA	NA	NA		NA	NA
Cross-lab validity	3;291	NA	Indirect	Consistent	Precise	CAP Report Data	NA	High

[a] Five studies (N = 3252) contributed data to the meta-analysis.

[b] Eleven studies (N = 8626) contributed to the meta-analysis)

Abbreviations: CI = confidence interval; N = number; NA = not applicable.

Table D-4. KRAS for colorectal carcinoma

Outcome	Study Design: No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Other	Result/ Effect Size (CI)	Strength of Evidence
Risk of Recurrence	Cohort studies: 5 (4,085)	Medium	Indirect	Consistent	Precise	NA	Wild type vs. mutated: HR, 1.02 (0.91 to 1.14); no association found in adjusted analyses;	Low
Cancer-specific mortality	2 (1,747)	Medium	Indirect	Inconsistent	Imprecise	NA	Wild type vs. mutated: HR, 1.30 (1.02 to 1.66) KRAS mutation for the association between KRAS mutation and CSS	Insufficient
Overall survival	Cohort studies: 10 (5,328)	Medium	Indirect	Inconsistent	Imprecise	NA	Wild type vs. mutated: HR, 1.22 (0.95 to 1.55);	Low
Decisions about treatment	0 (0)	NA	NA	NA	NA	NA	NA	Insufficient
Analytic Validity	5;576	Low	Direct	Consistent	Precise		NA	High
Sensitivity and specificity	5;576	Low	Direct	Consistent	Precise		NA	High
Positive and negative predictive value	5;576	Low	Direct	Consistent	Precise		NA	High
Cross-lab validity	5;747	Low	Direct	Consistent	Precise	CAP Report Data	NA	High

Abbreviations: CI = confidence interval; N = number; NA = not applicable.

Table D-5. BRAF for colorectal carcinoma

Outcome	Study Design: No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Other	Result/ Effect Size (CI)	Strength of Evidence
Risk of Recurrence	Cohort studies: 5 (4,106)	Medium	Indirect	Inconsistent	Imprecise	NA	Wild type vs. mutation: HR, 1.07 (0.76 to 1.52);	Low
Cancer-specific mortality	Cohort studies: 7 (5,409)	Medium	Indirect	Consistent (all trend for association of mutation with worse outcome)	CND	NA	Wild type vs. mutation: HR, 1.5 (1.27 to1.77) for the association between mutation and cancer-specific mortality	Insufficient
Overall survival	Cohort studies: 11 (7,610)	Medium	Indirect	Consistent	CND	NA	Wild type vs. mutation: HR 1.45 (1.29 to 1.62),) for the association between mutation and survival	Insufficient
Decisions about treatment	0 (0)	NA	NA	NA	NA	NA	NA	Insufficient
Analytic Validity	1;117	Medium	Direct	Consistency Unknown (Single Study)	Imprecise			Low
Sensitivity and specificity	1;117	Medium	Direct	Consistency Unknown (Single Study)	Imprecise			Low
Positive and negative predictive value	1;117	Medium	Direct	Consistency Unknown (Single Study)	Imprecise			Low
Cross-lab validity	3;533	NA	Direct	Consistent	Precise	CAP Report Data	NA	High

Abbreviations: CI = confidence interval; N = number; NA = not applicable.

Table D-6. Oncotype Dx colon multi-gene assay for colorectal carcinoma

Outcome	Study Design: No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Other	Result/ Effect Size (CI)	Strength of Evidence
Risk of Recurrence	Cohort: 1 (690)	Medium	Indirect	Unknown	Imprecise	NA	HR, 1.68 (1.18 to 2.38)	Insufficient
Cancer-specific mortality	0 (0)	NA	NA	NA	NA	NA	NA	Insufficient
Overall survival	0 (0)	NA	NA	NA	NA	NA	NA	Insufficient
Decisions about treatment	0 (0)[a]	NA	NA	NA	NA	NA	NA	Insufficient
Analytic Validity	1;NR	Medium	Indirect	Consistency Unknown (Single Study)	Precise		NA	Low
Sensitivity and specificity	NA	NA	NA	NA	NA		NA	NA
Positive and negative predictive value	NA	NA	NA	NA	NA		NA	NA
Cross-lab validity	NA	NA	NA	NA	NA		NA	NA

[a] We identified no low or medium risk of bias studies. But we found three studies rated as high[1] or unclear[2] risk of bias that evaluated decisions of a total of 221 physicians (502 patients)

Abbreviations: CI = confidence interval; N = number; NA = not applicable.

Table D-7. Oncotype Dx breast multi-gene assay for breast carcinoma

Outcome	Study Design: No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Other	Result/ Effect Size (CI)	Strength of Evidence
Risk of Recurrence	Cohort: 6 (N=3,222) Case-control: 1 (N=40)	Medium	Indirect	Consistent	Precise	None	2.97(2.19,4.02)[a] High Risk vs. Low Risk	Insufficient
Cancer-specific mortality	Cohort: 1 (N=668) Case-control: 1 (N=566)	Low	Indirect	Consistent	Imprecise	None	2.02(1.35, 3.00) High Risk vs. Low Risk	Low
Overall survival	Cohort: 1 (N=668)	Low	Indirect	Unknown	Unknown	None	HR, 1.77 (1.35 , 2.33) High Risk vs. Low Risk	Insufficient
Decisions about treatment	Cohort: 6 (N=990) Uncontrolled trial: 10 (N=1,261)	Low	Indirect	Consistent	Precise	None	~30% of tx decisions changed by test	Moderate
Analytic Validity	NA	NA	NA	NA	NA		NA	NA
Sensitivity and specificity	NA	NA	NA	NA	NA		NA	NA
Positive and negative predictive value	NA	NA	NA	NA	NA		NA	NA
Cross-lab validity	NA	NA	NA	NA	NA		NA	NA

[a] Four studies (N = 2327) contributed data to the meta-analysis.

Abbreviations: CI = confidence interval; N = number; NA = not applicable; tx = treatment.

Table D-8. Mammaprint multi-gene assay for breast carcinoma

Outcome	Study Design: No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Other	Result/ Effect Size (CI)	Strength of Evidence
Risk of Recurrence	Cohort: 6 (N=1,913)	Medium	Indirect	Consistent	Imprecise	None	2.84(2.11,3.82) For poor prognosis vs. good prognosis	Insufficient
Cancer-specific mortality	Cohort: 5 (N=1615)	Medium	Indirect	Consistent	Imprecise	None	3.3 (2.22, 4.9) for poor prognosis vs. good prognosis	Insufficient
Overall survival	Cohort: 1 (N = 144)	Medium	Indirect	Unknown (single study)	Unknown (single study)	None	HR, 1.67 (0.73, 3.82) for poor prognosis vs. poor prognosis	Insufficient
Decisions about treatment	Cohort: 1 (N=427)	Low	Indirect	Unknown (single study)	Unknown (single study)	None	NA	Insufficient
Analytic Validity	2;399	Medium	Indirect	Consistent	Imprecise		NA	Moderate
Sensitivity and specificity	2;399	Medium	Indirect	Consistent	Imprecise		NA	Moderate
Positive and negative predictive value	2;399	Medium	Indirect	Consistent	Imprecise		NA	Moderate
Cross-lab validity	1; 100	Low	Indirect	Consistent	Imprecise		NA	Low

Abbreviations: BRCA = breast cancer; CI = confidence interval; N = number; NA = not applicable.

Table D-9. Urovysion multi-gene assay for urinary bladder carcinoma

Outcome	Study Design: No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Other	Result/ Effect Size (CI)	Strength of Evidence
Risk of Recurrence	Cohort study: 2 (168)	Low	Indirect	Consistent	Imprecise	Actual adjusted data NR in the larger (N=126) study, just qualitative description	Association between mutation and risk of recurrence in 2 small studies;[a] no evidence that test use leads to improved outcomes	Insufficient
Cancer-specific mortality	0 (0)	NA	NA	NA	NA	NA	NA	Insufficient
Overall survival	0 (0)	NA	NA	NA	NA	NA	NA	Insufficient
Decisions about treatment	0 (0)	NA	NA	NA	NA	NA	NA	Insufficient
Analytic Validity	NA	NA	NA	NA	NA		NA	NA
Sensitivity and specificity	NA	NA	NA	NA	NA		NA	NA
Positive and negative predictive value	NA	NA	NA	NA	NA		NA	NA
Cross-lab validity	4;555	NA	Indirect	Consistent	Precise	CAP Report Data	NA	High

[a] One study (N=126) only reported unadjusted data, and reported that the association between FISH results and tumor recurrence "persisted after accounting for other disease factors (stage, grade, history of prior tumors, concomitant CIS, use of post-operative mitomycin, etc.) at all time points."

Abbreviations: CI = confidence interval; N = number; NA = not applicable.

References

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2. Srivastava G, Renfro LA, Behrens RJ, et al. Prospective evaluation of a 12-gene assay on treatment recommendations in patients with stage II colon cancer. ASCO Gastrointestinal Symposium; 2013 January; San Francisco, CA.