Molecular Pathology Testing To Estimate Prognosis for Common Cancers

The purpose of the MEDCAC is three-fold:

- to evaluate the usefulness of certain molecular pathology tests (biomarkers) in determining the likelihood of recurrence of the common cancers listed,
- determine if the tests changed physician decision making, and
- determine if the test results improved outcomes (impact of treatment decisions)

The MEDCAC will consider the prognostic uses of the biomarkers, i.e., the ability of the test to estimate the likelihood of recurrence. CMS is aware that several of the biomarkers mentioned in this MEDCAC are now also being used as predictive factors to estimate the likelihood of response to specific therapy. We have explored that arrangement in previous MEDCACs, and predictive uses are beyond the scope of this discussion.

We recognize that confusion may arise since prognostic test have been noted to "predict" recurrence. What we are trying to determine is if these tests, either alone or in combination with other prognostic factors, can be used to determine recurrence, note decision management based on results, and documentation of improved outcomes. The technology assessment is focused on prognostic uses and did not evaluate uses to predict response to a specific therapy. Emphasis will be placed on the test's clinical utility, though both analytic validity as well as clinical validity will be discussed.

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(AHRQ CANG0212)
(*http://www.cms.gov/Medicare/Coverage/DeterminationProcess/Downloads/id94TA.pdf*)

a) Key Questions ('KQ') considered by EPC for this Technology Assessment (TA):

KQ1. (*Over-arching question*) Is there direct evidence that using these tests (whether alone or in combination with traditional prognostic factors) changes physician decision-making and improves outcomes?
KQ2. Analytical validity: outcomes included sensitivity/specificity, interlab reproducibility, and quality control standards, among others.
KQ3. Clinical validity: outcomes included risk of local/distant recurrence (RRc), cancer-specific survival (CSS), and overall survival (OS).
KQ4. Clinical utility: a) changed physician decision-making, or; b) improved patient outcomes.
KQ5. Harms associated with treatment decisions that are informed by molecular pathology tests.

Note: TA findings about Abbott Labs' UroVysion ® test are not shown below, based on manufacturer's assertion that the test is not intended or marketed for prognostic use.

b) Summary of Major EPC findings from the TA Structured Abstract:

"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 (colorectal cancer) 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)."

"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."

c) Glossary:

Note: gene names (e.g., *BRAF*) are italicized below. Gene products (e.g., BRAF protein) are denoted without italicization.

Term:	Definition:
ALK	The *ALK* gene (Anaplastic lymphoma kinase) results from a translocation of genetic material from chromosome 5 to chromosome 2. Expression of *ALK* leads to an enzyme with tyrosine kinase activity. *ALK* may be found in various malignant conditions, including lymphomas and certain cancers, such as NSCLC (Adapted from OMIM, www.omim.org).
Analytical validity	For a medical test, its degree of technical performance in detecting or quantitating the analyte of interest (Adapted from EGAPP 2009; see http://www.nature.com/gim/journal/v11/n1/full/gim20092a.html).
BRAF	The gene *BRAF*, present in all individuals, is needed for the production of BRAF protein, a part of an important signaling pathway for cell growth. However, mutations in *BRAF* may lead to abnormal BRAF function, which can include stimulation of uncontrolled cell growth (Adapted from OMIM).
Clinical utility	For a medical test, the balance of benefits and harms when the test is used to influence patient management (Adapted from EGAPP 2009).
Clinical validity	For a medical test, the strength of association that determines the test's ability to accurately and reliably identify or predict the disease or condition of interest (Adapted from EGAPP 2009).
EGFR	The gene *EGFR*, present in all individuals, produces the RNA code for the epidermal growth factor receptor (EGFR), a cell-surface protein which, when bound to various growth factors, demonstrates tyrosine kinase enzymatic activity to initiate several sequences of signaling proteins. Activation of the EGFR receptor leads to diverse cellular functions, including cell proliferation, differentiation, motility, and survival, and affects tissue development. Mutations in *EGFR* may affect any of these cell functions (Adapted from OMIM).
Gene expression profile (GEP)	As a medical test, a set of measurements of messenger RNA production (expression) by multiple genes by a certain cell type (e.g., a cancer cell). The gene expression profile can be interpreted to show the relative activity of a set of target genes. Using data reduction techniques, a *score* may be derived from the set of measured gene expression data to reflect selected genomic activity with that cell type.
KRAS	The gene *KRAS*, present in all individuals, provides instructions for making a protein called K-Ras involved primarily in regulating cell division as part of a signaling pathway. The KRAS protein relays signals from outside the cell to the cell's nucleus. These signals instruct the cell to grow and divide or to mature and take on specialized functions (differentiate). The *KRAS* gene, a member of a class of genes known as oncogenes, has the potential when mutated to cause normal cells to become cancerous. (Adapted from NIH Genetics Home Reference at http://ghr.nlm.nih.gov/glossary/).
Medical decision-making	The process by which a physician reaches any conclusion(s) about what if any diagnostic or therapeutic intervention(s) are appropriate for further care of a patient with an illness or injury.

Term:	Definition:
Microsatellite instability	A microsatellite is "a short segment of DNA that are distributed throughout the genome, that consist of repeated sequences of usually two to five nucleotides, and that are often useful markers in studies of genetic linkage because they tend to vary from one individual to another". (NIH Glossary) A made-up example of a microsatellite might be the DNA sequence '…CAGCAGCAGCAGCAGCAG …' in which the repeating element is 'CAG'. "The presence of additional microsatellite alleles (repeated segments) in tumor cells … result(s) from the inherent susceptibility of these areas to such alterations and from mutations in the DNA mismatch repair mechanism that would normally correct these errors" (See also http://ghr.nlm.nih.gov/glossary=microsatellite).
MLH1 promoter methylation	The protein MLH1 helps repair mismatched segments of genomic DNA. Inactivation of the promoter region of the *MLH1* gene by methylation may lead to loss of MLH1 protein production, persistent DNA damage, such as MSI, which then may lead to disorders in cell growth and differentiation. Increased *MLH1* promoter methylation is believed to be associated with the hereditary non-polyposis colorectal cancer (HPNCC) syndrome.
Non-small cell lung cancer (NSCLC)	A collective term referring to all types of lung cancer except for 'small cell lung cancer', a particular variety of lung cancer.
Outcome	As applied to medical care, the condition or status of a patient after completion of medical intervention(s). Examples of outcomes of interest to Medicare include risk of disease recurrence, survival, avoidance of harm, and quality of life.
Predictive value	For a medical test, measures of clinical validity: - 'positive predictive value (PPV)', the ratio of the number of persons with a positive test result who have the disease or condition of interest, to the number of persons with a positive test result; or - 'negative predictive value (NPV)', the ratio of persons with a negative test result who do not have the disease or condition of interest, to the number of persons with a negative test result.
Proficiency testing (PT)	A program that provides individual laboratories with unknown specimens for testing. The participating laboratories analyze the specimens and return the results for evaluation. Each participating laboratory later receives a report of their performance as well as a report summarizing the results of all participating laboratories. (Adapted from College of American Pathologists (CAP) website).
Prognosis	"An estimate of the likely course and outcome of a disease. The prognosis of a patient diagnosed with cancer is often viewed as the chance that the disease will be treated successfully and that the patient will recover." (Quoted from NCI Fact Sheet at www.cancer.gov/cancertopics/factsheet/Support/prognosis-stats)
Sensitivity	For a medical test, the ratio of the number of persons with a disease or condition of interest, who have a positive test result, to the number of persons with the disease or condition of interest.
Specificity	For a medical test, the ratio of the number of persons who do not have a disease or condition of interest and who have a negative test result, to the number of persons with the disease or condition of interest.

d) **Crosswalk between Technology Assessment Key Questions and MEDCAC Questions**

Technology Assessment Key Questions (KQs)	MEDCAC Voting Questions
KQ1. (*Over-arching question*) Is there direct evidence that using these tests (whether alone or in combination with traditional prognostic factors) changes physician decision-making and improves outcomes?	3. How confident are you that there is sufficient evidence to conclude that using the molecular pathology test to estimate prognosis has clinical utility (meaning, that it ***improves*** health outcomes either due to increased benefits and/or reduced harms) for Medicare beneficiaries with cancer whose anti-cancer treatment strategy is guided by the test's result?
KQ2. Analytical validity: outcomes included sensitivity/specificity, interlab reproducibility, and quality control standards, among others.	1.a) For each prognostic test listed above, how confident are you that existing evidence is sufficient to confirm the analytical validity of the molecular pathology test to estimate prognosis for Medicare beneficiaries with that cancer type?
KQ3. Clinical validity: outcomes included risk of local/distant recurrence (RRc), cancer-specific survival (CSS), and overall survival (OS).	1.b) For each prognostic test listed above, how confident are you that existing evidence is sufficient to confirm the clinical validity of the molecular pathology test to estimate prognosis in Medicare beneficiaries with that cancer type?
KQ4. Clinical utility: a) changed physician decision-making, or; b) improved patient outcomes. KQ5. Harms associated with treatment decisions that are informed by molecular pathology tests.	2. How confident are you that there is sufficient evidence to conclude that using the molecular pathology test to estimate prognosis ***affects*** health outcomes (including benefits and harms) for Medicare beneficiaries with cancer whose anti-cancer treatment strategy is guided by the test's result?

4. MEDCAC Discussion Question: Do any of the following four factors affect generalizability of evidence about of prognostic molecular diagnostic tests?
   a) Regulatory status of test (e.g., US Food & Drug Administration (FDA) approved/cleared vs. laboratory-developed test)?
   b) Type of performing laboratory (i.e., university medical center laboratories, independent commercial laboratories, or community hospital-based laboratories)?
   c) Subgroups in the Medicare beneficiary population (e.g., by age)?
   d) Genomic variations within cancers (e.g., diversity of cancer genomes)?