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Cancer Network®

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May 21, 2019

Katherine B. Szarama, PhD
Lead Analyst
Coverage and Analysis Group
Centers for Medicare & Medicaid Services
7500 Security Blvd.
Baltimore, MD 21244

RE: National Coverage Analysis (NCA) Tracking Sheet for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450R)

Dear Dr. Szarama:

The National Comprehensive Cancer Network® (NCCN®) is pleased to comment on the National Coverage Analysis (NCA) Tracking Sheet for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450R), as it relates to the evidence available for tests of germline mutations to identify those with hereditary cancer who may benefit from targeted treatments based on results of the tests.

As an alliance of 28 leading academic cancer centers in the United States that treat hundreds of thousands of patients with cancer annually, NCCN is a developer of authoritative information regarding cancer prevention, screening, diagnosis, treatment, and supportive care that is widely used by clinical professionals and payers alike. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a comprehensive set of guidelines detailing the sequential management decisions and interventions that currently apply to 97 percent of cancers affecting patients in the United States. NCCN Guidelines® and Library of Compendia products help ensure access to appropriate care, clinical decision-making, and assessment of quality improvement initiatives.

The NCCN Drugs & Biologics Compendium (NCCN Compendium®) has been recognized by the Centers for Medicare and Medicaid Services (CMS) and clinical professionals in the commercial payer setting since 2008 as an evidence-based reference for establishment of coverage policy and coverage decisions regarding off-label use of anticancer and cancer-related medications. Further, NCCN Guidelines and Library of Compendia products are utilized by commercial payers that represent more than 85 percent of covered lives in the United States.

NCCN thanks CMS for reopening the NCA process in response to the healthcare community's concerns regarding recent coverage boundaries on a patient's ability to access clinically appropriate NGS-based testing for germline mutations. In particular, applying the 2018 NCD to NGS-based testing for hereditary breast, ovarian, and colorectal cancer syndromes to only patients with advanced cancer contradicts clinically appropriate care outlined in evidence-based guidelines and would adversely impact cancer prevention, detection, care, and outcomes. Given that CMS referenced NCCN Guidelines in the Proposed Decision Memorandum's

Discussion of Evidence (CAG-00450N), we encourage CMS to incorporate clinically relevant recommendations from the NCCN Guidelines® for Genetic/Familial High-Risk Assessment: Colorectal, the NCCN Guidelines® for Genetic/Familial High-Risk Assessment: Breast and Ovarian, and the NCCN Guidelines® for Breast Cancer Risk Reduction presented below into the final coverage policy.

Family studies have long documented an increased risk for several forms of cancer among first-degree relatives (i.e., parents, siblings, children) and second-degree relatives (i.e., grandparents, aunts or uncles, grandchildren, nieces or nephews) of affected individuals. Cancers developing in these individuals may be classified as hereditary or familial cancers. These individuals may have an increased susceptibility to cancer as the result of one or more gene mutations present in parental germline cells, and often require intensive cancer surveillance, screening, or consideration of preventative medical therapies. Multi-gene testing for hereditary forms of cancer has rapidly altered the clinical approach to testing at-risk patients and their families. Based on NGS technology, these tests simultaneously analyze a set of genes that are associated with a specific family cancer phenotype or multiple phenotypes. Multiple studies have shown that this approach may detect pathogenic or likely pathogenic variants not found in single-gene testing.¹⁻⁴ A study of 198 women referred for BRCA1/2 testing who underwent multi-gene testing showed 16 additional deleterious mutations out of 141 women who tested negative specifically for BRCA1/2 (11.4%; 95% CI, 7.0–17.7).² The discovery of these mutations led to recommendations for further screening. Therefore, findings from multigene testing have the potential to alter clinical management.⁵

When more than one gene can explain an inherited cancer syndrome, then multi-gene testing may be more efficient and/or cost-effective than single-gene testing. For example, though breast cancer is mainly associated with BRCA1/2 pathogenic or likely pathogenic variants, it may also be associated with variants in the following genes: ATM, BARD1, CHEK2, PALB2, STK11, CDH1, PTEN, and TP53.^{1; 6-9} In these cases where more than one pathogenic or likely pathogenic variant could potentially influence a condition, multi-gene testing would be clinically relevant and cost-effective.¹⁰⁻¹²

Clinically appropriate recommendations from the NCCN Guidelines for Genetic/Familial High-Risk Assessment and NCCN Guidelines for Risk Reduction should be used as a reference tool when understanding patient populations that would benefit from NGS tests of germline mutations. Both the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal and the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian provide clinical criteria, independent of the disease stage or presence of disease, for individuals with an increased genetic risk who could benefit from NGS-based quantification for hereditary cancers (Appendix 1 and Appendix 2). Once clinical criteria for multi-gene testing of germline mutations is met, the NCCN Guidelines outline specific management algorithms that might include intensive cancer surveillance, screening, or consideration of preventative medical therapies. For example, the NCCN Guidelines for Breast Cancer Risk Reduction recommend evidence-based options, including risk-reducing surgery or targeted therapies, for women with an elevated predisposition to breast cancer identified by NGS-based testing for hereditary cancers and who desire risk-reducing therapy (Appendix 3). Lastly, recognizing that multi-

gene testing might not be clinically appropriate for all individuals, the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian provide examples of clinical scenarios for which multi-gene testing should not be considered and syndrome-specific panels may be preferred (Appendix 2).

We would urge CMS to clarify the current NCA so that coverage for NGS-based testing for germline mutations, when supported by evidence-based clinical practice guidelines, is not compromised as a result of broad restrictions to NGS-based testing under the NCD. NCCN again appreciates the opportunity to comment on CMS' NCA for NGS for Medicare beneficiaries with advanced cancer as it relates to NGS-based testing for germline mutations. We would welcome the opportunity to discuss our comments further and look forward to working together to ensure access to high quality, high value care for patients with cancer. Thank you for your time and consideration of our comments.

Sincerely,



Robert W. Carlson, MD
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National Comprehensive Cancer Network
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References

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National Comprehensive
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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Genetic/Familial High-Risk Assessment: Breast and Ovarian

Version 3.2019 — January 18, 2019

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ASSESSMENT

Patient needs and concerns:

- Knowledge of genetic testing for cancer risk, including benefits, risks, and limitations
- Goals for cancer family risk assessment

Detailed family history:

- Expanded pedigree, particularly around individuals with a diagnosis of cancer, to include a three-generational pedigree ([See BR/OV-B](#))
- Types of cancer, bilaterality, age at diagnosis
- History of chemoprevention and/or risk-reducing surgery
- Medical record documentation as needed, particularly prior genetic testing results for patients and their family members and pathology reports of primary cancers

Detailed medical and surgical history:

- Any personal cancer history (eg, age, histology, laterality)
- Carcinogen exposure (eg, history of radiation therapy)
- Reproductive history
- Hormone or oral contraceptive use
- Previous breast biopsies and pathology results
- History of salpingo-oophorectomy

Focused physical exam (conducted by qualified clinician):

- Cowden syndrome/PTEN hamartoma tumor syndrome (PHTS) specific:
 - ▶ Dermatologic,^j including oral mucosa
 - ▶ Head circumference
 - ▶ Thyroid (enlarged or nodular on palpation)

GENE TESTING^k

See Targeted Testing Criteria for
[BRCA-Related Breast/Ovarian Cancer
Syndrome \(BRCA-1\)](#)

[Li-Fraumeni Syndrome \(LIFR-1\)](#)

[Cowden Syndrome/PHTS \(COWD-1\)](#)

[See Multi-Gene Testing \(GENE-1\)](#)

^jFor Cowden syndrome dermatologic manifestations, [see COWD-1](#) and for PJS dermatologic manifestations, [see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal](#).

^kIn some cases, multi-gene testing may be a preferable way to begin testing over the single-gene testing process.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



BRCA1/2 TESTING CRITERIA^{a,b}

Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management.

Testing of an individual without a cancer diagnosis should only be considered when an appropriate affected family member is unavailable for testing.

- Individual from a family with a known *BRCA1/2* pathogenic/likely pathogenic variant, including such variants found on research testing^d
- Personal history of breast cancer^e + one or more of the following:
 - ◊ Diagnosed ≤45 y
 - ◊ Diagnosed 46-50 y with:
 - ◊ An additional breast cancer primary at any age^d
 - ◊ ≥1 close blood relative^e with breast cancer at any age
 - ◊ ≥1 close blood relative^e with high-grade (Gleason score ≥7) prostate cancer
 - ◊ An unknown or limited family history^a
 - ◊ Diagnosed ≤60 y with:
 - ◊ Triple-negative breast cancer
 - ◊ Diagnosed at any age with:
 - ◊ ≥1 close blood relative^e with:
 - breast cancer diagnosed ≤50 y; or
 - ovarian carcinoma^f; or
 - male breast cancer; or
 - metastatic prostate cancer^g; or
 - pancreatic cancer
 - ◊ ≥2 additional diagnoses^d of breast cancer at any age in patient and/or in close blood relatives
- Ashkenazi Jewish ancestry^h
- Personal history of ovarian carcinoma^f

^aFor further details regarding the nuances of genetic counseling and testing, see [BR/COCA](#).

^bIrrespective of degree of relatedness.

^cFor the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.

^dTwo breast cancer primaries includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors diagnosed either synchronously or asynchronously.

^eClose blood relatives include first-, second-, and third-degree relatives on same side of family. (See [BR/COCA](#).)

^fIncludes fallopian tube and primary peritoneal cancers. *BRCA*-related ovarian cancers are associated with epithelial, non-mucinous histology. Lynch syndrome can be associated with both non-mucinous and mucinous epithelial tumors. Be attentive for clinical evidence of Lynch syndrome (see [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal](#)). Specific types of non-epithelial ovarian cancers and tumors can also be associated with other rare syndromes. Examples include an association between sex-cord tumors with annular tubules and Peutz-Jeghers syndrome or Sertoli-Leydig tumors and DICER1-related disorders.

- Personal history of male breast cancer
- Personal history of pancreatic cancerⁱ
- Personal history of metastatic prostate cancer^g
- Personal history of high-grade prostate cancer (Gleason score ≥7) at any age with:
 - ◊ ≥1 close blood relatives^e with ovarian carcinoma, pancreatic cancer, or metastatic prostate cancer^g at any age or breast cancer <50 y; or
 - ◊ ≥2 close blood relatives^e with breast, or prostate cancer (any grade) at any age; or
 - ◊ Ashkenazi Jewish ancestry^h
- *BRCA1/2* pathogenic/likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline pathogenic/likely pathogenic variant analysis
- Regardless of family history, some individuals with an *BRCA*-related cancer may benefit from genetic testing to determine eligibility for targeted treatment^j
- An individual who does not meet the other criteria but with ≥1 first- or second-degree blood relative^k meeting any of the above criteria. The significant limitations of interpreting test results for an unaffected individual should be discussed.

^gMetastatic prostate cancer is biopsy-proven and/or with radiographic evidence and includes distant metastasis and regional bed or nodes. It is not a biochemical recurrence.

^hTesting for Ashkenazi Jewish founder-specific pathogenic/likely pathogenic variant(s), should be performed first. Comprehensive genetic testing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or if other *BRCA*-related criteria are met. Founder pathogenic/likely pathogenic variants exist in other populations.

ⁱApproximately 2%–5% of unselected cases of pancreatic adenocarcinoma will have a *BRCA1/2* pathogenic/likely pathogenic variant. However, the disease is highly lethal and the option to test the affected relative may not be available in the future. Thus, there may be significant benefit to family members in testing these patients near the time of diagnosis. In addition, increasing evidence suggests that identification of a *BRCA1/2* pathogenic/likely pathogenic variant may direct use of targeted therapies for patients with pancreatic cancer (see [NCCN Guidelines for Pancreatic Adenocarcinoma](#)). (Holler S, Borgida A, Dodd A, et al. *J Clin Oncol* 2015;33:3124–3129. Shindo K, Yu J, Suenaga M, et al. *J Clin Oncol* 2017;35:3382–3390.)

^jEg. PARP inhibitors for ovarian cancer and metastatic HER2-negative breast cancer; platinum therapy for prostate cancer. See the relevant NCCN treatment guidelines (eg, [NCCN Guidelines for Breast Cancer](#), [NCCN Guidelines for Prostate Cancer](#)) for further details.

^kThis may be extended to an affected third-degree relative if related through two male relatives (eg, paternal grandfather's mother or sister).

BRCA
testing
criteria
met

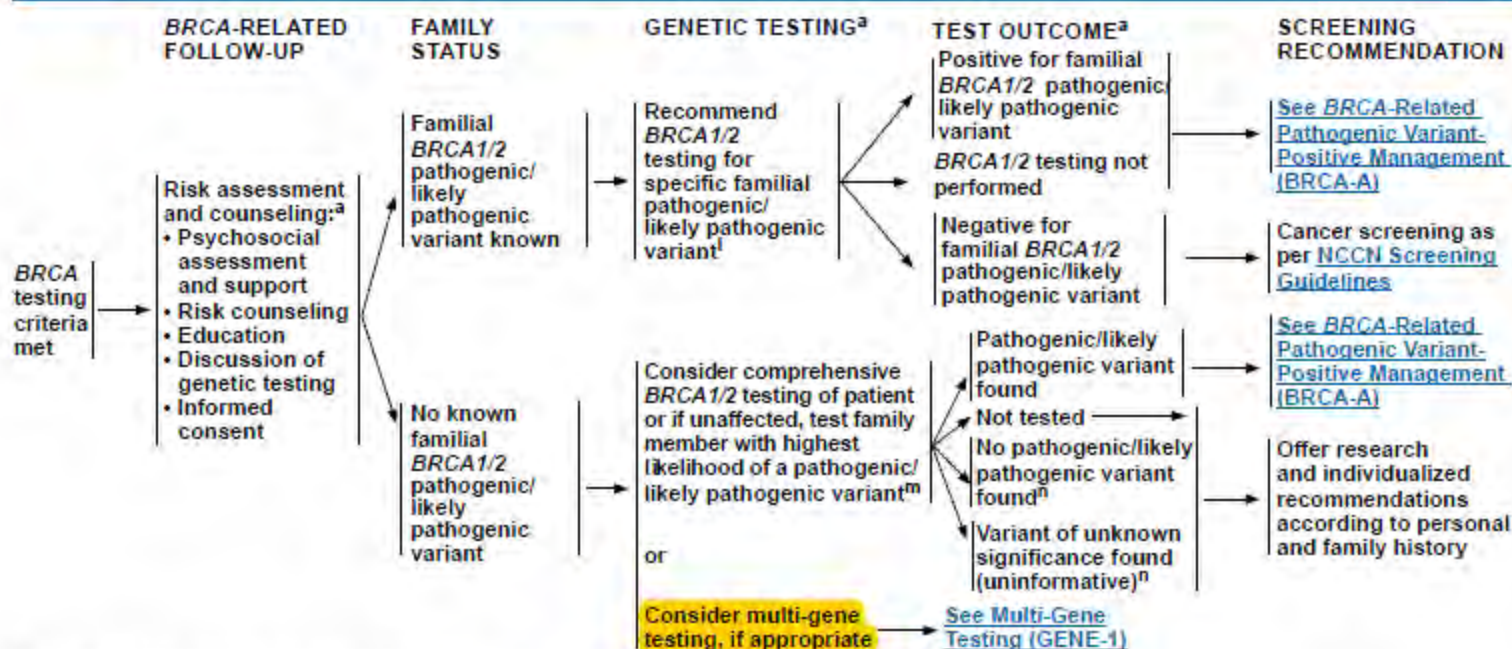
See
Follow-up
([BRCA-2](#))

If *BRCA*
testing
criteria
not met,
consider
testing
for other
hereditary
syndromes

If criteria
for other
hereditary
syndromes
not met,
then cancer
screening
as per
[NCCN
Screening
Guidelines](#)

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



^aFor further details regarding the nuances of genetic counseling and testing, see [BR/OV-A](#).

^bIf of Ashkenazi Jewish descent, in addition to the specific familial pathogenic/likely pathogenic variant, test for all three founder pathogenic/likely pathogenic variants. Additional testing may be indicated if there is also a significant family history of cancer on the side of the family without the known pathogenic/likely pathogenic variant.

^mFor both affected and unaffected individuals of Ashkenazi Jewish descent with no known familial pathogenic/likely pathogenic variant, first test for the three common pathogenic variants. Then, if negative for the three pathogenic/likely pathogenic variants and ancestry also includes non-Ashkenazi Jewish relatives or other BRCA-related criteria are met, consider comprehensive genetic testing. For both affected and unaffected individuals who are non-Ashkenazi Jewish and who have no known familial pathogenic/likely pathogenic variants, comprehensive genetic testing is the approach, if done.

ⁿIf no pathogenic/likely pathogenic variant is found, consider testing another family member with next highest likelihood of having a pathogenic/likely pathogenic variant and/or other hereditary breast/ovarian cancer syndromes such as Li-Fraumeni ([LIFR-1](#)) and/or Cowden syndrome ([COWD-1](#)) or multi-gene testing ([GENE-1](#)). For additional information on other genetic pathogenic/likely pathogenic variants associated with breast/ovarian cancer risk for which genetic testing is clinically available, see [GENE-2](#).

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MULTI-GENE TESTING

Overview of multi-gene testing

- The recent introduction of multi-gene testing for hereditary forms of cancer has rapidly altered the clinical approach to testing at-risk patients and their families. Based on next-generation sequencing technology, these tests simultaneously analyze a set of genes that are associated with a specific family cancer phenotype or multiple phenotypes.
- Patients who have a personal or family history suggestive of a single inherited cancer syndrome are most appropriately managed by genetic testing for that specific syndrome. When more than one gene can explain an inherited cancer syndrome, then multi-gene testing may be more efficient and/or cost-effective.
- There may be a role for multi-gene testing in individuals who have tested negative (indeterminate) for a single syndrome, but whose personal or family history remains suggestive of an inherited susceptibility.
- As commercially available tests differ in the specific genes analyzed (as well as classification of variants and many other factors), choosing the specific laboratory and test panel is important.
- Multi-gene testing can include “intermediate” penetrant (moderate-risk) genes.^a For many of these genes, there are limited data on the degree of cancer risk and there are no clear guidelines on risk management for carriers of pathogenic/likely pathogenic variants. Not all genes included on available multi-gene tests are necessarily clinically actionable.
- As is the case with high-risk genes, it is possible that the risks associated with moderate-risk genes may not be entirely due to that gene alone, but may be influenced by gene/gene or gene/environment interactions. In addition, certain pathogenic/likely pathogenic variants in a gene may pose higher or lower risk than other pathogenic/likely pathogenic variants in that same gene. Therefore, it may be difficult to use a known pathogenic/likely pathogenic variant alone to assign risk for relatives.
- In many cases the information from testing for moderate penetrance genes does not change risk management compared to that based on family history alone.
- Pathogenic/likely pathogenic variants in many breast cancer susceptibility genes involved in DNA repair may be associated with rare autosomal recessive conditions.
- There is an increased likelihood of finding variants of unknown significance when testing for pathogenic/likely pathogenic variants in multiple genes.
- It is for these and other reasons that multi-gene testing is ideally offered in the context of professional genetic expertise for pre- and post-test counseling.

^aResearch is evolving, and gene carriers should be encouraged to participate in clinical trials or genetic registries.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

[References](#)

[Continued](#)

Appendix 2: Selected excerpts from NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (Version 1.2018) referencing Multi-Gene Testing



NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Genetic/Familial High-Risk Assessment: Colorectal

Version 1.2018 — July 12, 2018

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MULTI-GENE TESTING

Table 3: Examples of Clinical Scenarios for Which Multi-Gene Testing Should and Should Not Be Used

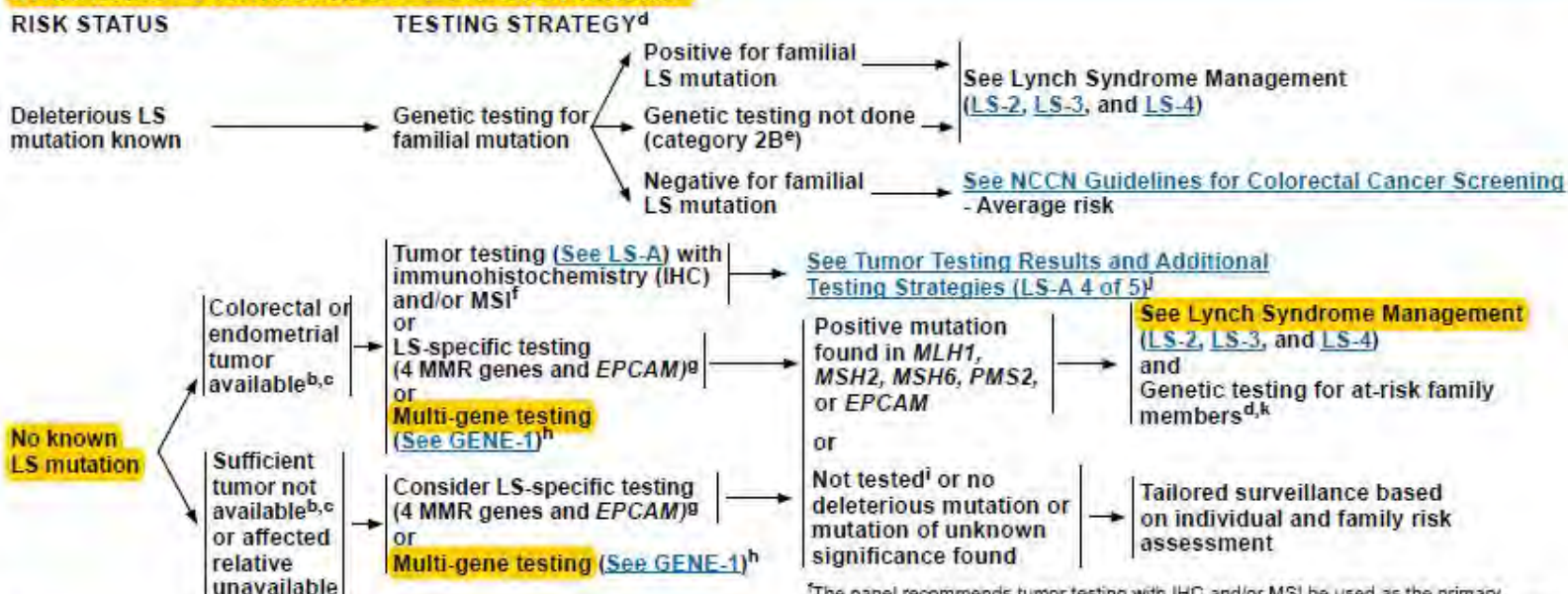
<p>Examples of clinical scenarios for which multi-gene testing should be considered:</p> <ul style="list-style-type: none">• Personal medical and/or family cancer history meets criteria for more than one hereditary cancer syndrome (ie, family meets both <i>BRCA</i>-related breast and/or ovarian cancer and LS clinical criteria or family history of young-onset CRC and oligopolyposis)• Colonic polyposis with uncertain histology• Family cancer history does not meet established testing guidelines, but consideration of inherited cancer risk persists and an appropriate panel is available• Individuals concerned about cancer predisposition for whom family cancer history is limited or unknown• Second-line testing for inherited cancer risk when first-line testing has been inconclusive• Adenomatous polyposis (<i>APC</i>, <i>MUTYH</i>, <i>POLE</i>, <i>POLD1</i>)
<p>Examples of clinical scenarios for which multi-gene testing SHOULD NOT be considered:^b</p> <ul style="list-style-type: none">• An individual from a family with a known mutation and no other reason for multi-gene testing• As first-line testing when the family history is strongly suggestive of a known hereditary syndrome

^bSyndrome-specific panels may be appropriate.

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[Continued](#)

STRATEGIES FOR EVALUATING FOR LYNCH SYNDROME^{a,d}



^aThe panel recommends universal screening of all CRCs to maximize sensitivity for identifying individuals with Lynch syndrome and to simplify care processes. Counseling by an individual with expertise in genetics is not required prior to routine tumor testing. An infrastructure needs to be in place to handle the screening results.

^bCriteria that may justify LS testing include meeting Bethesda Guidelines (See Discussion), Amsterdam Criteria (See Discussion), cancer diagnosis prior to age 50, or having a predicted risk for Lynch syndrome >5% on one of the following prediction models: MMRpro, PREMM5, or MMRpredict.

^cIf there is more than one affected family member, first consider: youngest age at diagnosis, multiple primaries, and colorectal or endometrial cancers. Limitations of interpreting test results should be discussed if testing tumors other than colorectal or endometrial cancers. If IHC/MSI previously done, see LS-A 4 of 5.

^dProper pretest counseling should be done by an individual with expertise in genetics.

^eThe recommendation to manage patients in whom genetic testing was not done using LS-management recommendations is category 2B.

^fThe panel recommends tumor testing with IHC and/or MSI be used as the primary approach for pathology-lab-based universal screening. If tumor is available, LS-specific testing or multi-gene testing without IHC or MSI should only be utilized in select cases under direction of a clinician with expertise in genetics, and should not be used as a universal testing strategy.

^gThe decision to test all 4 MMR genes and EPCAM concurrently versus sequentially (stepwise) is left to the discretion of the clinician.

^hThis approach may be preferred in patients with a strong family history or if diagnosed age <50 y (Pearlman R, et al. JAMA Oncol 2017;3:464-471; Yurgelun M, et al. J Clin Oncol 2017;35:1086-1095).

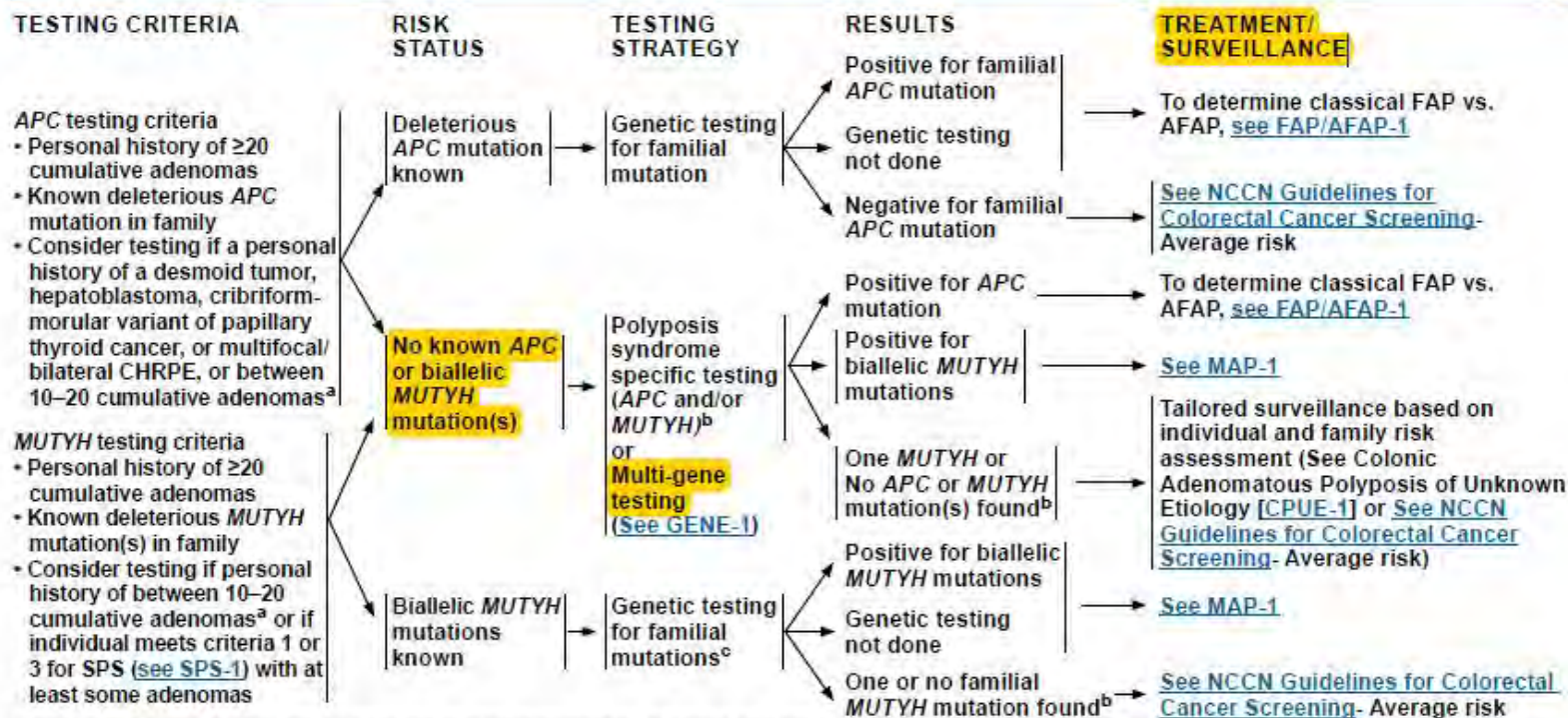
ⁱTesting of unaffected family members when no affected member is available should be considered. Significant limitations of interpreting test results should be discussed.

^jFor individuals found to have a deleterious LS mutation, see LS management recommendations.

^kAn at-risk family member can be defined as a first-degree relative of an affected individual and/or proband. If a first-degree relative is unavailable or unwilling to be tested, more distant relatives should be offered testing for the known mutation in the family.

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^aAge of onset, family history, and/or presence of other features may influence whether genetic testing is offered in these situations.

^bWhen colonic polyposis is present in a single person with a negative family history, consider testing for a *de novo* APC mutation; if negative, follow with testing of MUTYH (targeted testing for the two common northern European founder mutations c.536A>G and c.1187G>A may be considered first followed by full sequencing if biallelic mutations are not found). When colonic polyposis is present only in siblings, consider recessive inheritance and test for MUTYH first. Order of testing for APC and MUTYH is at the discretion of the clinician. MUTYH genetic testing is not indicated based on a personal history of a hepatoblastoma, cribriform-morular variant of papillary thyroid cancer, or multifocal/bilateral CHRPE.

^cSiblings of a patient with MAP are recommended to have site-specific testing for the familial mutations. Full sequencing of MUTYH may be considered in an unaffected parent when the other parent has MAP. If the unaffected parent is found to not have a MUTYH mutation, genetic testing in the children is not necessary to determine MAP status. If the unaffected parent is not tested, comprehensive testing of MUTYH should be considered in the children. If the unaffected parent is found to have one MUTYH mutation, testing the children for the familial MUTYH mutations is indicated.

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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Breast Cancer Risk Reduction

Version 1.2019 — December 11, 2018
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FAMILIAL RISK ASSESSMENT^a

Familial/genetic factors

- Known genetic predisposition to breast cancer (*BRCA1/2*, *p53*, *PTEN*, or other gene mutation)

→ [See BRISK-2](#)

- Criteria for further genetic risk evaluation for women with no personal history of invasive breast cancer or ductal carcinoma in situ (DCIS)^b
[See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian](#)

Woman meets one or more of the familial/genetic risk criteria outlined in [NCCN Guidelines for Genetic/Familial Assessment Breast and Ovarian](#)

Yes →

Referral to genetic counselor or a similarly trained professional recommended^c
AND
[See BRISK-2](#)

No →

[See BRISK-3](#)

^aSee [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian](#).

^bThe criteria for further genetic risk assessment and genetic testing are not identical. For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included. The maternal and paternal sides of the family should be considered independently for familial patterns of cancer.

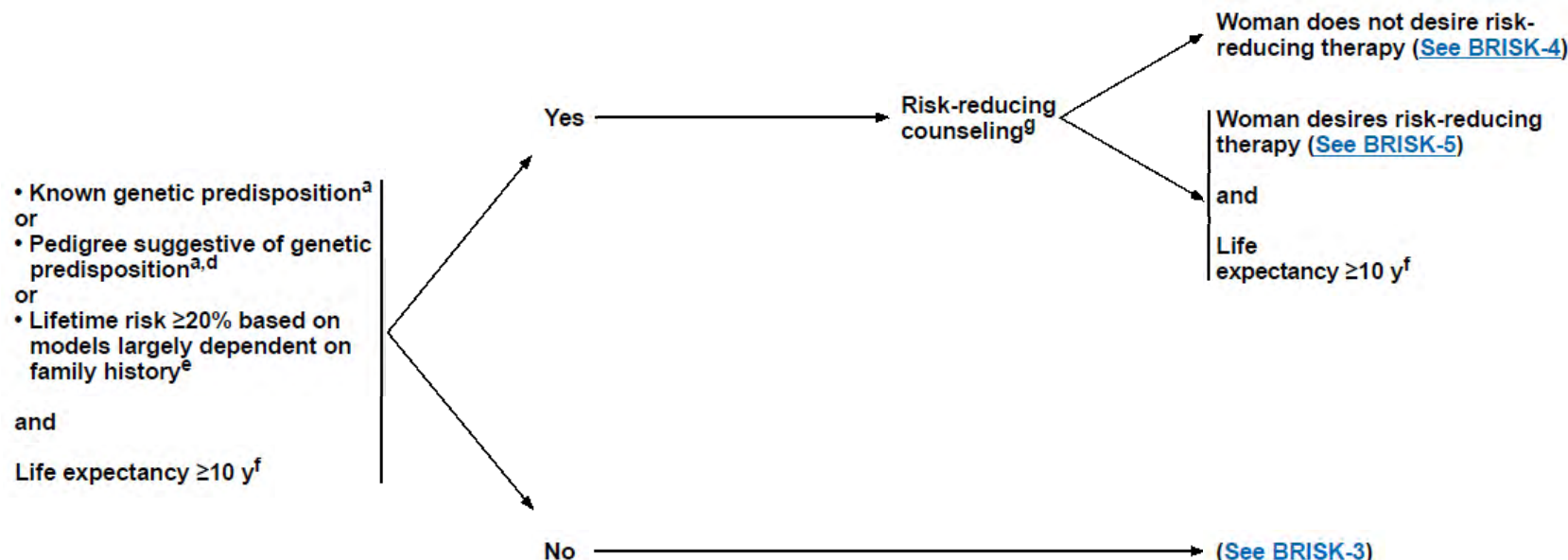
^cFor further details regarding the nuances of genetic counseling and testing, see [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian--BR/OV-A](#).

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ADDITIONAL RISK ASSESSMENT



^aSee [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian](#).

^dWoman meets one or more of the familial risk criteria (See BRISK-1).

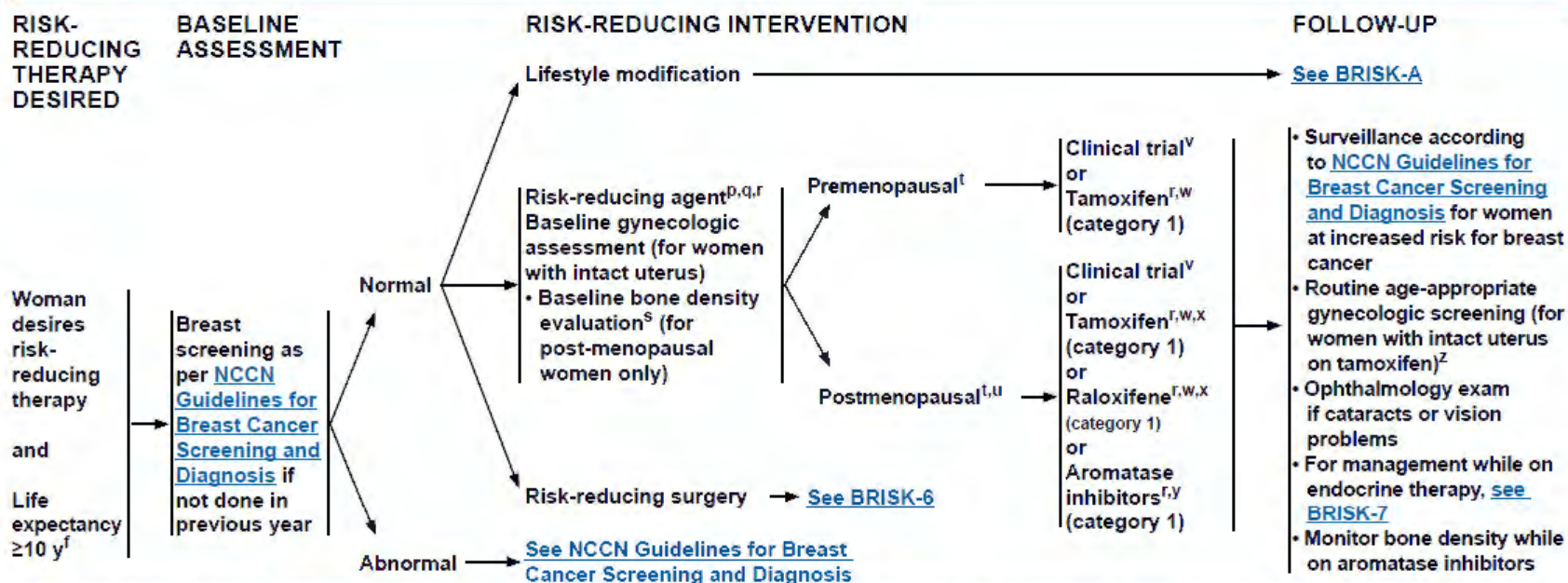
^eRisk models that are largely dependent on family history (eg, Claus, BRCAPRO, BOADICEA, Tyrer-Cuzick).

^fSee life expectancy calculator (www.epronosis.com). For a reference point, the life expectancy of the average 78-year-old woman in the United States is 10.2 years. (See [NCCN Guidelines for Older Adult Oncology](#)).

^gSee [Components of Risk/Benefit Assessment and Counseling \(BRISK-A\)](#).

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



^fSee life expectancy calculator (www.epronosis.com). For a reference point, the life expectancy of the average 78-year-old woman in the United States is 10.2 years. ([See NCCN Guidelines for Older Adult Oncology](#)).

^pThere are no data regarding the use of risk-reducing agents in women with prior thoracic RT.

^qCYP2D6 genotype testing is not recommended in women considering tamoxifen.

^rSee [Breast Cancer Risk-Reducing Agents \(BRISK-B\)](#).

^sTo guide choice of risk-reducing therapy (eg, low baseline bone density—choose raloxifene over aromatase inhibitors).

^tClinical trials in breast cancer have utilized a variety of definitions of menopause.

Menopause is generally the permanent cessation of menses, and as the term is utilized in breast cancer management includes a profound and permanent decrease in ovarian estrogen synthesis. Reasonable criteria for determining menopause include any of the following: Prior bilateral oophorectomy; age ≥ 60 years; age < 60 years and amenorrhea for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and follicle-stimulating hormone (FSH) and estradiol in the postmenopausal range. If taking tamoxifen or toremifene and age < 60 y, reasonable criteria include FSH and plasma estradiol level in postmenopausal ranges.

^uBone density may play a role in choice of therapy.

^vWomen in clinical trial should have baseline exam, follow-up, and monitoring as per protocol.

^wUtility of tamoxifen or raloxifene for breast cancer risk reduction in women < 35 years of age is unknown. Raloxifene is only for post-menopausal women > 35 years. While raloxifene in long-term follow-up appears to be less efficacious in risk reduction than tamoxifen, consideration of toxicity may still lead to the choice of raloxifene over tamoxifen in women with an intact uterus. Tamoxifen is a teratogen and is contraindicated during pregnancy or in women planning a pregnancy.

^xWhen counseling postmenopausal women regarding the risk/benefit of tamoxifen and raloxifene, refer to tables in Freedman AN, et al. Benefit/risk assessment for breast cancer chemoprevention with raloxifene or tamoxifen for women age 50 years or older. J Clin Oncol 2011;29(17):2327-2333.

^yExemestane and anastrozole are not currently FDA-approved for breast cancer risk reduction. There are currently no data comparing the benefits and risks of exemestane and anastrozole to those of tamoxifen or raloxifene. If tamoxifen or raloxifene is contraindicated, (eg, thromboembolic events), aromatase inhibitors may be considered.

^zRoutine endometrial ultrasound and biopsy are not recommended for women in the absence of other symptoms.

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