November 27, 2019

Tamara Syrek Jensen, JD  
Director  
Coverage and Analysis Group  
Centers for Medicare & Medicaid Services  
7500 Security Boulevard  
Baltimore, MD 21244

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

Dear Ms. Syrek Jensen:

The National Comprehensive Cancer Network® (NCCN®) is pleased to comment on the Proposed Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450R) as it relates to evidence supporting the use of NGS for identification of germline mutations.

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. NCCN’s mission is to improve and facilitate quality, effective, efficient, and accessible cancer care so patients can live better lives. 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.

The NCCN Biomarkers Compendium® is a tool developed to identify the appropriate use of biomarkers to screen, diagnose, monitor, and provide predictive and prognostic
information for the treatment of patients. Based directly on the NCCN Guidelines, the NCCN Biomarkers Compendium contains information designed to support decision-making around the use of biomarker testing in patients with cancer. The goal of the NCCN Biomarkers Compendium is to provide essential details for those tests which have been approved by NCCN Guidelines Panels and are recommended by the NCCN Guidelines. Tests that measure changes in genes or gene products and which are used for diagnosis, screening, monitoring, surveillance, or for providing predictive or prognostic information are included in the NCCN Biomarkers Compendium. General information on appropriate methodologies for biomarker testing is provided, focusing on the biology or abnormality being measured rather than on commercially available tests or test kits. The NCCN Biomarkers Compendium aims to ensure that patients have coverage and access to appropriate biomarker testing based on the evaluations and recommendations of NCCN Guidelines Panel members.

**NCCN Evidence Base and Guidelines Development Process**

The proposed decision memo inaccurately states that the NCCN Guidelines® are not evidence-based. As such, NCCN would like to provide clarifying information on our guidelines development process and the evidence-base for our guideline recommendations. The NCCN Guidelines are composed of recommendations based on the best evidence available at the time they are derived. NCCN library of guidelines contain 28,000 references to evidence. Additionally, the guidelines submitted for consideration, Genetic/Familial High-Risk Assessment Breast and Ovarian and Genetic/Familial High-Risk Assessment: Colorectal, contain respectively 508 and 255 references to evidence.

The development of the NCCN Guidelines is an ongoing and iterative process based on a critical review of the best available evidence and derivation of recommendations by a multidisciplinary panel of experts in the field of cancer. Because new data are published continuously, it is essential that the NCCN Guidelines also be continuously updated and revised to reflect new data and new clinical information. The NCCN Guidelines are reviewed and updated on a continual basis to ensure that the recommendations take into account the most current evidence. All active NCCN Guidelines are reviewed and updated at least annually. In 2018, NCCN published 185 guideline updates to ensure guidelines reflect the most up-to-date and comprehensive evidence available.

The annual review process is driven largely by the annual Institutional Review performed for each of the NCCN Guidelines. However, interim Panel meetings are conducted throughout the year, as needed, based upon new evidence from studies evaluating existing agents or regulatory approvals of new drugs or biologics that may change clinical practice standards.
Recommendations within the NCCN Guidelines are derived from critical evaluation of evidence, integrated with the clinical expertise and consensus of a multidisciplinary panel of cancer specialists, clinical experts and researchers in those situations where high-level evidence does not exist. Panels are charged with evaluating the efficacy of treatment, utility of tests or evaluations, and toxicity of the various interventions. Recommendations or changes to existing recommendations are agreed upon by Panel Members following review and discussion of the evidence during the Panel meetings. The Panel Members deliberate on the interpretation of the clinical evidence, and vote on how the evidence should be incorporated into the existing Guidelines.

**NCCN Guideline References within Proposed Decision Memo**

NCCN would like to emphasize the clear distinction between tumor testing for patient therapeutic guidance in our cancer specific guidelines, as opposed to germline testing noted in our Genetic/Familial High-Risk recommendations to inform risk-reduction and screening in affected individuals and their family members. Within the proposed decision memo, CMS cites submitted NCCN guidelines but lists information derived from NCCN’s Breast Cancer Guidelines and Ovarian Cancer Guidelines rather than the Genetic/Familial High-Risk Assessment Breast and Ovarian Guidelines. The NCCN Breast Cancer Guidelines and Ovarian Cancer Guidelines include treatment recommendations based on germline mutation status. However, the information contained within the current NCCN Breast Cancer Guidelines that CMS cites is not relevant to the clinical utility of NGS for germline testing, as these Guidelines provide no mention of NGS for germline mutation testing. Additionally, the information included from the NCCN Ovarian Cancer Guidelines pertains to NGS for tumor testing only. Like the breast cancer treatment guidelines, the ovarian cancer treatment guidelines provide no mention of NGS for germline mutation testing. NCCN respectfully requests that CMS refer to and consider recommendations in the Genetic/Familial High-Risk Assessment Breast and Ovarian and Genetic/Familial High-Risk Assessment: Colorectal Guidelines. In addition, NCCN respectfully requests that CMS remove the content from the treatment guidelines that are currently cited within the proposed decision memo.

Both the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal and the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian recommend that multi-gene testing be offered in the context of professional genetic expertise, with pre- and post-test counseling being offered. 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. Besides breast and ovarian cancers, the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian also recommend consideration of multi-gene germline testing in the context of pancreatic cancer, which is thought to have a familial or hereditary component in approximately 10% of cases.¹²
Finally, CMS does not include the submitted Genetic/Familial High-Risk Assessment: Colorectal Guidelines within this section, although it was submitted. NCCN notes that there is evidence to support germline multi-gene testing in patients with colorectal cancer in certain clinical circumstances. Examples of clinical scenarios for which multi-gene testing should be considered include:\(^3\)

- Personal medical and/or family cancer history meets criteria for more than one hereditary cancer syndrome (i.e., family meets both BRCA-related breast and/or ovarian cancer and Lynch Syndrome clinical criteria or family history of young-onset colorectal cancer 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

Clinically appropriate recommendations from the NCCN Guidelines for Genetic/Familial High-Risk Assessment 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. In the proposed decision memo, CMS states that studies on colorectal cancer and Lynch syndrome were not included in the evidence review because the studies did not assess mortality. NCCN notes that timely identification of individuals at risk for hereditary cancers offers an opportunity to intervene to prevent the development of cancer which may ultimately impact mortality.
Proposed Decision Memo Language

CMS proposes to cover NGS testing for patients with ovarian or breast cancer, clinical indications for germline testing, risk factors for germline breast or ovarian cancer, who have not been previously tested using NGS. Additionally, CMS proposes to allow Medicare Administrative Contractors (MACs) to cover NGS testing when for patients with a cancer diagnosis other than breast or ovarian cancer, clinical indications for germline testing, risk factors for germline cancer other than inherited breast or ovarian cancer, and who have not been previously tested using NGS. NCCN agrees with CMS that there is evidence to support NGS testing in patients with breast and ovarian cancer. Additionally, NCCN notes there is data available to support NGS for germline testing for hereditary syndromes associated with pancreas and colon cancers.¹,²,³

NCCN has heard concerns from patient advocacy groups that the proposed decision memo as currently worded may cause confusion among providers. Specifically, the proposed decision memo states that a patient must have breast or ovarian cancer, and clinical indications for germline testing, and risk factors for germline testing. FORCE specifically notes that, for instance, all women with ovarian cancer meet clinical guidelines for germline testing. NCCN agrees with FORCE in their comments that this language may be confusing or duplicative.

NCCN has also heard concern from both providers and patient advocacy groups that as written, the proposed decision memo indicates coverage only of NGS tests that are FDA approved or cleared for germline testing. To date, none of the NGS products on the market are approved specifically for germline testing and are unable to distinguish between germline and somatic mutations. As such, NCCN agrees with the concern of patient and provider groups that this requirement may cause patient access issues.

Additionally, patient advocates have expressed concern about limiting patients to one NGS test. NCCN recommends updating the language to cover additional NGS testing when the panel incorporates new or different potentially pathogenic variants.

NCCN suggests that simplifying the NCD language will address the issues noted above and make the language more appropriate for germline testing rather than somatic testing. NCCN proposes CMS revise the NCD language to read:

A. The Centers for Medicare & Medicaid Services (CMS) proposes that the evidence is sufficient to expand coverage of Next Generation Sequencing (NGS) as a diagnostic laboratory test when performed in a CLIA-certified laboratory, when ordered by a treating physician for management of the patient and when all the following conditions are met:

The patient has:
• clinical indications for germline (inherited) testing,

• risk factors for germline (inherited) cancer, and

• not been previously tested using NGS, or if the proposed panel incorporates new or different potentially pathogenic variants

NCCN again appreciates the opportunity to comment on CMS’ Proposed Decision Memo for NGS for Medicare beneficiaries with advanced cancer as it relates to evidence supporting the use of NGS for identification of germline mutations. NCCN requests that CMS consider coverage consistent with nationally recognized, continuously updated, and evidence-based guidelines such as the NCCN Guidelines to ensure Medicare beneficiaries have access to the most up-to-date recommendations. Additionally, NCCN respectfully requests that CMS remove references to the Breast and Ovarian Cancer treatment guidelines and instead refer to the NCCN Genetic/Familial High-Risk Assessment Breast and Ovarian Guidelines and the NCCN Genetic/Familial High-Risk Assessment: Colorectal Guidelines. Additionally, NCCN encourages CMS to consider revised wording in the proposed decision memo that would not impede patient access to clinically appropriate germline multi-gene testing.

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
Chief Executive Officer
National Comprehensive Cancer Network
carlson@nccn.org  215.690.0300
References


APPENDIX 1
For Cowden syndrome dermatologic manifestations, see COWD-1 and for PJS dermatologic manifestations, see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.

In 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 CRITERIAa,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 testingb.**
- **Personal history of breast cancerc + one or more of the following:**
  - **Diagnosed ≤45 y**
  - **Diagnosed 46-50 y with:**
    - An additional breast cancer primary at any aged
    - ≥1 close blood relativee with breast cancer at any age
    - ≥1 close blood relativee with high-grade (Gleason score ≥7) prostate cancer
    - An unknown or limited family historya
  - **Diagnosed ≤50 y with:**
    - Triple-negative breast cancer
  - **Diagnosed at any age with:**
    - ≥1 close blood relativee with:
      - breast cancer diagnosed ≤50 y; or
      - ovarian carcinoma; or
      - male breast cancer; or
      - metastatic prostate cancer; or
      - pancreatic cancer
    - ≥2 additional diagnosised of breast cancer at any age
  - **Ashkenazi Jewish ancestryf**
  - **Personal history of ovarian carcinoma**

- **Personal history of male breast cancer**
- **Personal history of pancreatic canceri**
- **Personal history of metastatic prostate cancer**
- **Personal history of high-grade prostate cancer**
  - (Gleason score ≥7) at any age with
    - ≥1 close blood relativesi with ovarian carcinoma, pancreatic cancer, or metastatic prostate cancer at any age or breast cancer <50 y; or
    - ≥2 close blood relativesi with breast, or prostate cancer (any grade) at any age; or
    - Ashkenazi Jewish ancestry
- **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 treatmentk**
- **An individual who does not meet the other criteria but with ≥1 first- or second-degree blood relativek meeting any of the above criteria. The significant limitations of interpreting test results for an unaffected individual should be discussed.**

For further details regarding the nuances of genetic counseling and testing, see BR/ OV-A.

a,bRespective 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/OV-B)

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.

9Metastatic 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.

iTesting 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.

jApproximately 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). (Holter 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.)

kBPARP 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).

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.
**BRCA-Related Breast and/or Ovarian Cancer Syndrome**

<table>
<thead>
<tr>
<th>FAMILY STATUS</th>
<th>GENETIC TESTING</th>
<th>TEST OUTCOME</th>
<th>SCREENING RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Familial BRCA1/2 pathogenic/likely pathogenic variant known</strong></td>
<td>Recommend BRCA1/2 testing for specific familial pathogenic/likely pathogenic variant</td>
<td>Positive for familial BRCA1/2 pathogenic/likely pathogenic variant</td>
<td>See BRCA-Related Pathogenic Variant-Positive Management (BRCA-A)</td>
</tr>
<tr>
<td><strong>No known familial BRCA1/2 pathogenic/likely pathogenic variant</strong></td>
<td>Consider comprehensive BRCA1/2 testing of patient or if unaffected, test family member with highest likelihood of a pathogenic/likely pathogenic variant</td>
<td>Negative for familial BRCA1/2 pathogenic/likely pathogenic variant</td>
<td>Cancer screening as per NCCN Screening Guidelines</td>
</tr>
<tr>
<td></td>
<td>Consider multi-gene testing, if appropriate</td>
<td>Pathogenic/likely pathogenic variant found</td>
<td>See BRCA-Related Pathogenic Variant-Positive Management (BRCA-A)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not tested</td>
<td>Offer research and individualized recommendations according to personal and family history</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No pathogenic/likely pathogenic variant found</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Variant of unknown significance found (uninformative)</td>
<td></td>
</tr>
</tbody>
</table>

**BRCA testing criteria met**

- Risk assessment and counseling:
  - Psychosocial assessment and support
  - Risk counseling
  - Education
  - Discussion of genetic testing
  - Informed consent

**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.

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For further details regarding the nuances of genetic counseling and testing, see BR/OV-A.

If 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.

For both affected and unaffected individuals of Ashkenazi Jewish descent with no known familial BRCA1/2 pathogenic/likely pathogenic variant, first test for the three common 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.

If 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.
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.

\(^a\)Research is evolving, and gene carriers should be encouraged to participate in clinical trials or genetic registries.
Genetic/Familial High-Risk Assessment: Breast and Ovarian

and management. The counselor should recommend genetic counseling and testing for at-risk relatives. Since some pathogenic or likely pathogenic variants are associated with rare autosomal recessive conditions (e.g., Fanconi anemia is associated with ATM, BRCA2, BRIP1, and PALB2 variants), testing of a partner of a carrier of a pathogenic or likely pathogenic variant may be considered to inform reproductive decision-making. See Table 3 for a list of pathogenic/likely pathogenic variants associated with autosomal recessive conditions.

Multi-Gene Testing

Next-generation sequencing allows for the sequencing of multiple genes simultaneously. This is referred to as multi-gene testing. Multi-gene testing for hereditary forms of cancer has rapidly altered the clinical approach to testing at-risk patients and their families. Multi-gene testing simultaneously analyzes 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. A study of 198 women referred for BRCA1/2 testing who underwent multi-gene testing showed 16 deleterious mutations out of 141 women who tested negative for BRCA1/2 (11.4%; 95% CI, 7.0–17.7). The discovery of these mutations led to recommendations for further screening. Therefore, findings from multi-gene testing have the potential to alter clinical management.

Multi-gene testing could include only high-penetrance genes associated with a specific cancer, or both high- and moderate-penetrance genes. Comprehensive cancer risk panels, which include a large number of genes associated with a variety of cancer types, are also available. The decision to use multi-gene testing for patient care should be no different than the rationale for testing a single gene known to be associated with the development of a specific type of cancer. Testing is focused on identifying a pathogenic or likely pathogenic variant known to be clinically actionable; that is, whether the management of an individual patient is altered based on the presence or absence of the variant. Multi-gene testing may be most useful when more than one gene can explain an inherited cancer syndrome. For example, though ovarian cancer is mainly associated with BRCA1/2 pathogenic or likely pathogenic variants, it may also be associated with variants in the following genes: BARD1, BRIP1, MRE11A, MSH2, MSH6, NBN, PALB2, RAD51C, RAD51D, and TP53. Genes associated with hereditary breast cancer include the following that could potentially be included in a multi-gene test: BRCA1/2, ATM, BARD1, CHEK2, PALB2, TP53, PTEN, STK11, and CDH1. In these cases where more than one pathogenic or likely pathogenic variant could potentially influence a condition, multi-gene testing may be more efficient and/or cost-effective. Multi-gene testing may also be considered for those who tested negative (indeterminate) for one particular syndrome, but whose personal and family history is suggestive of an inherited susceptibility.

There are several issues to consider regarding multi-gene testing. First, commercially available tests may differ significantly on a number of factors, such as number of genes analyzed, turnaround time, insurance coverage, and variant reclassification protocol, among others. Tests requiring a longer turnaround time may not be suitable for patients who need rapid results. The specific laboratory and multi-gene test should be chosen carefully. Second, in some cases, next-generation sequencing may miss some pathogenic or likely pathogenic variants that would have been detected with traditional single-gene analysis. Third, pathogenic or likely pathogenic variants identified for more than one gene add complexity that may lead to difficulty in making risk management recommendations. A management plan should only be developed for identified pathogenic or likely pathogenic variants that are clinically actionable.
A major dilemma regarding multi-gene testing is that there are limited data and a lack of clear guidelines regarding degree of cancer risk associated with some of the genes assessed in multi-gene testing, and how to communicate and manage risk for carriers of these genes.\textsuperscript{73,79-82} This issue is compounded by the low incidence rates of hereditary disease, leading to a difficulty in conducting adequately powered studies.\textsuperscript{79} Some multi-gene tests may include moderate-penetrance genes, for which there are little available data regarding degree of cancer risk and guidelines for risk management.\textsuperscript{66,73,83-85} Further, it is possible that the risks associated with these genes may not entirely be due to that gene only, but may be influenced by gene/gene or gene/environment interactions. Also, certain variants in a gene may be associated with a different degree of risk than other variants in that gene. For example, the presence of certain \textit{ATM} genetic variants is associated with an increased risk for early-onset breast cancer and frequent bilateral occurrence, but the association between other \textit{ATM} variants and breast cancer susceptibility is less clear.\textsuperscript{86-89}

As a result of these dilemmas, risk management following detection of a pathogenic or likely pathogenic variant for a moderate-risk gene, and how best to communicate risk to relatives, is currently unknown.\textsuperscript{85,90} Further, the information gained from testing for moderate-penetrance genes may not change risk management recommendations significantly compared to that based on family history only. Multi-gene tests also increase the likelihood of detecting a VUS.\textsuperscript{63,64,66,73,74,85,91} Multi-gene analyses of DNA samples from individuals with breast cancer showed that a VUS was found in 33\% to 40\% of individuals.\textsuperscript{74} An analysis of 1191 individuals who underwent testing and were enrolled in PROMPT showed that 37\% of variants found were classified as a VUS.\textsuperscript{54} The considerable possibility of detecting a VUS adds to the complexity of counseling following multi-gene testing. However, as multi-gene testing is increasingly used, the frequency of a VUS being detected is expected to decrease.

Multi-gene testing is a new and rapidly growing field, but there is currently a lack of evidence regarding proper procedures and risk management strategies that should follow testing, especially when pathogenic or likely pathogenic variants are found for moderate-penetrance genes and when a VUS is found.\textsuperscript{92} For this reason, the NCCN Panel recommends that, when multi-gene testing is offered, it is done in the context of professional genetic expertise, with pre- and post-test counseling being offered. Panel recommendations are in agreement with recommendations by ASCO, which issued an updated statement regarding genetic testing in 2015.\textsuperscript{93} Given the limited data available in this field, carriers of a pathogenic or likely pathogenic variant should be encouraged to participate in clinical trials or genetic registries.

**Hereditary Breast or Breast/Ovarian Cancer Syndromes**

Breast cancer is the most frequently diagnosed cancer globally and is the leading cause of cancer death in women.\textsuperscript{94} The ACS estimates that 255,180 Americans will be diagnosed with invasive breast cancer and 41,070 will die of the disease in the United States in 2017.\textsuperscript{95} Up to 10\% of breast cancers are due to specific mutations in single genes that are passed down in a family.\textsuperscript{6,8,69,75} Specific patterns of hereditary breast/ovarian cancers are linked to pathogenic or likely pathogenic variants in the \textit{BRCA1}/\textit{2} genes.\textsuperscript{96,97} In addition, two very rare hereditary cancer syndromes exhibiting an increased risk for breast cancer are Li-Fraumeni syndrome (LFS) and Cowden syndrome, which are related to germline pathogenic or likely pathogenic variants in the \textit{TP53} and \textit{PTEN} genes, respectively.\textsuperscript{98,99} Similar to the \textit{BRCA1}/\textit{2} genes, the \textit{TP53} and \textit{PTEN} genes encode for proteins involved in processes related to tumor suppression, such as DNA repair and cell cycle regulation.

These hereditary syndromes share several features beyond elevation of breast cancer risk. These syndromes arise from germline pathogenic or likely pathogenic variants that are not within sex-linked genes; hence, the


APPENDIX 2
## STRATEGIES FOR EVALUATING FOR LS IN INDIVIDUALS MEETING CRITERIA FOR THE EVALUATION OF LS

### RISK STATUS

<table>
<thead>
<tr>
<th>LS pathogenic variant known(^b) in family</th>
<th>Genetic testing for familial pathogenic variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal or endometrial tumor available for proband or family(^c)</td>
<td>Tumor testing (See LS-A) with immunohistochemistry (IHC), MSI,(^d) and/or a comprehensive tumor NGS panel(^e) or Germline multi-gene testing (See GENE-1)(^f,g)</td>
</tr>
<tr>
<td>Sufficient tumor not available(^c) or affected relative unavailable</td>
<td>Germline multi-gene testing (See GENE-1)(^f,g)</td>
</tr>
</tbody>
</table>

### TESTING STRATEGY\(^a\)

| Positive for familial LS pathogenic variant | See Lynch Syndrome Management (LS-2, LS-3, and LS-4) and Genetic testing for at-risk family members\(^a,j\) |
| Genetic testing not done (category 2B\(^h\)) | See NCCN Guidelines for Colorectal Cancer Screening - Additional testing may be indicated based on personal and family medical history |
| Negative for familial LS pathogenic variant | See Tumor Testing Results and Additional Testing Strategies (LS-A 4 of 5)\(^i\) |

| Positive pathogenic variant found | See appropriate gene in Table 5 on GENE-7 and Genetic testing for at-risk family members\(^a,j\) or |
| Not tested or no pathogenic variant or variant of uncertain significance found | Tailored surveillance based on individual and family risk assessment |

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\(^a\) An individual with expertise in genetics should be involved in the testing process. Minimum pretest counseling (in person or through written or video) materials with pros and cons of testing should be provided. See Principles of Cancer Risk Assessment and Counseling (HRS-A 1 of 6).

\(^b\) Irrespective of degree of relatedness.

\(^c\) If 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.

\(^d\) The panel recommends tumor testing with IHC and/or MSI be used as the primary approach for pathology lab-based universal screening.

\(^e\) Tumor NGS panels should include at a minimum the MMR genes (MLH1, MSH2, MSH6, PMS2, and EPCAM), other known familial cancer genes, MSI, and BRAF.


\(^g\) Testing of unaffected family members when no affected member is available should be considered. Significant limitations of interpreting test results should be discussed.

\(^h\) The recommendation to manage patients in whom genetic testing was not done using LS-management recommendations is category 2B.

\(^i\) For individuals found to have an LS pathogenic variant, see LS management recommendations.

\(^j\) If a first-degree relative is unavailable or unwilling to be tested, more distant relatives should be offered testing for the known pathogenic variant in the family.

---

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.
### Adenomatous Polyposis Testing Criteria

<table>
<thead>
<tr>
<th>Risk Status</th>
<th>Testing Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic variant(s) known</td>
<td>Genetic testing for familial pathogenic variant</td>
</tr>
<tr>
<td>No known pathogenic variants in any polyposis gene</td>
<td>Germline multi-gene testing (preferred)</td>
</tr>
</tbody>
</table>

#### RESULTS

- Positive for familial *APC* pathogenic variant
- Positive for biallelic *MUTYH* pathogenic variant
- Positive for known familial pathogenic variant in another polyposis gene
- Genetic testing not done
- Negative for familial pathogenic variant
- One familial *MUTYH* pathogenic variant found
- Positive for familial *APC* pathogenic variant
- Positive for biallelic *MUTYH* pathogenic variant
- Positive for pathogenic variant in another polyposis gene
- No pathogenic variant found in any polyposis gene
- Genetic testing not done
- One *MUTYH* pathogenic variant found

#### TREATMENT/SURVEILLANCE

- To determine classical FAP vs. AFAP, see FAP/AFAP-1
- See MAP-1
- See GENE-7
- Manage as if positive for the known familial pathogenic variant
- See NCCN Guidelines for Colorectal Cancer Screening - Additional testing may be indicated based on personal and family medical history
- To determine classical FAP vs. AFAP, see FAP/AFAP-1
- See MAP-1
- See GENE-7
- Tailored surveillance based on individual and family risk assessment (See CPUE-1 or See NCCN Guidelines for Colorectal Cancer Screening - Average risk)
- See CPUE-1
- See GENE-7

---

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.

---

\(^a\) Irrespective of degree of relatedness.
\(^b\) Age of onset, family history, personal history of colorectal cancer, and/or presence of other features may influence whether genetic testing is offered in these situations.
\(^c\) There are clinically relevant yet rarer genes that can cause a polyposis that may be phenotypically indistinguishable from APC/MUTYH polyposis.
\(^d\) Multi-gene panel should include all polyposis and colorectal cancer genes (Stanich P, et al. Clin Gastroenterol Hepatol 2018).
\(^e\) When colon polyposis is present in a single person with a negative family history, consider testing for a de novo *APC* pathogenic variant; if negative, follow with testing of *MUTYH* (targeted testing for the two common northern European founder pathogenic variants c.536A>G and c.1187G>A may be considered first followed by full sequencing if biallelic pathogenic variants 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* testing is not indicated based on a personal history of a hepatoblastoma, cribriform-morular variant of papillary thyroid cancer, or multifocal/bilateral CHRPE.

\(^f\) Siblings of a patient with MAP are recommended to have site-specific testing for the familial pathogenic variants. Full sequencing of *MUTYH* may be considered in an unaffected parent when the other parent has MAP. If the unaffected parent is found to have one *MUTYH* pathogenic variant, testing the children for the familial *MUTYH* pathogenic variants is indicated. If the unaffected parent is not tested, comprehensive testing of *MUTYH* should be considered in the children. Testing for children of *MUTYH* heterozygotes should be offered if the other parent is also a heterozygote or could still be offered if the other parent is not a heterozygote and management would change (if they have an FDR affected with CRC) or inform reproductive risks (since their future children could be at-risk for MAP).
### Multi-Gene Testing

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

<table>
<thead>
<tr>
<th>Examples of clinical scenarios for which multi-gene testing should be considered:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Personal medical and/or family cancer history meets criteria for more than one hereditary cancer syndrome (i.e., family meets both \emph{BRCA}-related breast and/or ovarian cancer and \emph{LS} clinical criteria or family history of young-onset CRC and oligopolyposis)</td>
</tr>
<tr>
<td>• Colonic polyposis with uncertain histology</td>
</tr>
<tr>
<td>• Family cancer history does not meet established testing guidelines, but consideration of inherited cancer risk persists and an appropriate panel is available</td>
</tr>
<tr>
<td>• Individuals concerned about cancer predisposition for whom family cancer history is limited or unknown</td>
</tr>
<tr>
<td>• Second-line testing for inherited cancer risk when first-line testing has been inconclusive</td>
</tr>
<tr>
<td>• Adenomatous polyposis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Examples of clinical scenarios for which multi-gene testing SHOULD NOT be considered:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• An individual from a family with a known pathogenic variant and no other reason for multi-gene testing</td>
</tr>
<tr>
<td>• As first-line testing when the family history is strongly suggestive of a known hereditary syndrome</td>
</tr>
</tbody>
</table>

\(^\text{f} \) Syndrome-specific panels may be appropriate.

---

\( \text{Note: All recommendations are category 2A unless otherwise indicated. } \)

\( \text{Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged. } \)
Colonic Adenomatous Polyposis of Unknown Etiology (CPUE-1)

When genetic testing in an individual with polyposis reveals no APC and one or no MUTYH mutations, surveillance should be tailored based on individual and family risk assessment, as outlined in the guidelines. If the patient has a history of ≥100 adenomas, the panel recommends that the patient be managed as described above for patients with a personal history of classical FAP.

If the patient has a history of >20 but <100 adenomas, and the adenoma burden is small and considered to be manageable by colonoscopy and polypectomy, the panel recommends colonoscopy and polypectomy every 1 to 2 years. Clearing of all polyps is recommended and can be repeated at short intervals if residual polyps are present.

If the patient has a history of >20 but <100 adenomas, but the adenoma burden is dense and considered unmanageable by polypectomy, the panel recommends a subtotal colectomy. A proctocolectomy may be considered if there is a dense rectal polyposis that cannot be managed by polypectomy.

In patients with a family history of ≥100 adenomas diagnosed at age <40 years in a first-degree relative, there are limited data to suggest definitive recommendations for when to initiate screening or the interval of screening. The panel suggests considering colonoscopy screenings and polypectomy every 2 to 3 years starting at the same age as the youngest diagnosis of polyposis in the family if uncomplicated by cancer or by age 40 years, whichever is earliest. If multiple polyps are found during screenings, the interval for colonoscopies should occur every 1 to 3 years, depending on the type, number, and size of polyps. As described above, family members affected with polyposis should consider genetic testing as previously described for FAP and MAP.

In patients with a family history of >20 to <100 adenomas diagnosed at age ≥40 years in a first-degree relative, there are limited data to suggest definitive recommendations for when to initiate screening or the interval of screening. The panel suggests considering colonoscopy screenings and polypectomy every 2 to 3 years starting at age 40 years if uncomplicated by cancer. If multiple polyps are found during screenings, the interval for colonoscopies should occur every 1 to 3 years, depending on the type, number, and size of polyps. As described above, family members affected with polyposis should consider genetic testing as previously described for FAP and MAP.

Multi-gene Testing (GENE-1)

Next-generation sequencing allows for the sequencing of multiple genes simultaneously. This is referred to as multi-gene testing. The NCCN panel added information regarding multi-gene testing for the 2016 update. 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. Multi-gene testing simultaneously analyzes a set of genes that are associated with a specific family cancer phenotype or multiple phenotypes. Multi-gene testing may include syndrome-specific tests (ie,
panels that test for only one syndrome like Lynch syndrome), cancer-specific tests (ie, panels that test for more than one gene associated with a specific type of cancer like CRC), and comprehensive cancer panels (ie, panels that test for more than one gene associated with multiple cancers or cancer syndromes).

Multi-gene testing could include only high-penetrance genes associated with a specific cancer, or both high- and moderate-penetrance genes. Comprehensive cancer risk panels, which include a large number of genes associated with a variety of cancer types, are also available. The decision to use multi-gene testing for patient care should be no different than the rationale for testing a single gene known to be associated with the development of a specific type of cancer. Testing is focused on identifying a mutation known to be clinically actionable; that is, whether the management of an individual patient is altered based on the presence or absence of a mutation. Multi-gene testing may be most useful when more than one gene can explain a patient’s clinical and family history. In these cases where more than one gene mutation could potentially influence a condition, multi-gene testing may be more efficient and/or cost-effective. Multigene testing with panels that include genes associated with Lynch syndrome, as well as other highly penetrant genes associated with CRC, may be cost effective, and this approach may detect mutations not found in single-gene testing. Multi-gene testing may also be considered for those who tested negative (indeterminate) for one particular syndrome, but whose personal and family history is strongly suggestive of an inherited susceptibility.

A major dilemma regarding multi-gene testing is that there are limited data and a lack of clear guidelines regarding degree of cancer risk associated with some of the genes assessed in multi-gene testing, and how to communicate and manage risk for carriers of these genes. This issue is compounded by the low incidence rates of hereditary disease, leading to a difficulty in conducting adequately powered studies. Some multi-gene tests may include low or moderate-penetrance genes, for which there are little available data regarding degree of cancer risk and guidelines for risk management. Further, it is possible that the risks associated with these genes may not be due entirely to that gene only, but may be influenced by gene/gene or gene/environment interactions. Multi-gene tests also increase the likelihood of detecting VUS, with likelihood rates ranging from 17% to 38%. The considerable possibility of detecting a VUS adds to the complexity of counseling following multi-gene testing. However, as multi-gene testing is increasingly used, the frequency of a VUS being detected is expected to decrease.

There are other issues to consider regarding multi-gene testing. First, commercially available tests may differ significantly on a number of factors, such as number of genes analyzed, turnaround time, and insurance coverage, among others. Tests requiring a longer turnaround time may not be suitable for patients who need rapid results. The specific laboratory and multi-gene test should be chosen carefully. In some cases, next-generation sequencing may miss some mutations that would have been detected with traditional single-gene analysis. Third, mutations identified for more than one gene add complexity that may lead to difficulty in making risk management recommendations. A management plan should only be developed for identified gene mutations that are clinically actionable; care should be taken to ensure that overtreatment or overscreening does not occur due to findings for which clinical management is uncertain, or findings that are incorrectly interpreted due to lack of evidence.

Multi-gene testing is a new and rapidly growing field, but there is currently a lack of evidence regarding proper procedures and risk management strategies that should follow testing, especially when mutations are found for moderate-penetrance genes and when a VUS is
found. For this reason, the NCCN panel recommends that multi-gene testing be offered in the context of professional genetic expertise, with pre- and post-test counseling being offered. Panel recommendations are in agreement with recommendations by ASCO, which issued an updated statement regarding genetic testing in 2015. Carriers of a genetic mutation should be encouraged to participate in clinical trials or genetic registries.

Multi-gene testing is not recommended when: 1) there is an individual from a family with a known mutation and there is no other reason for multi-gene testing; 2) the patient’s family history is strongly suggestive of a known hereditary syndrome; and, 3) the patient is diagnosed with CRC with MSI or loss of one or more DNA MMR proteins. In these three scenarios, syndrome-specific panels may be considered.

Multi-gene testing may be considered (but may not be limited to based on clinical judgement) the following scenarios:

- A patient has a personal or family history that meets criteria for more than one hereditary cancer syndrome (eg, Lynch syndrome and BRCA-related breast and/or ovarian cancer)
- Colonic polyposis with uncertain histology
- Adenomatous polyposis (specific to APC, MUTYH, POLE, and POLD1)
- Family history does not meet criteria for established testing guidelines, but there is suspicion of hereditary cancer, and an appropriate panel is available
- Family history is limited or unknown, but patient has concerns about hereditary cancer
- As second-line testing when first-line testing is inconclusive

Emerging evidence has identified additional genes that may be associated with increased risk for CRC, and the panel has evaluated the strength of the evidence based on published reports. For example, there is well-established evidence that the I1307K polymorphism in the APC gene, found in people of Ashkenazi Jewish decent, predisposes carriers to CRC. Data are emerging for other genes associated with increased risk for CRC, though the data may not be as robust. For instance, one GREM1 single nucleotide polymorphism (SNP) (rs16969881) has been shown to be associated with increased risk for CRC. Additionally, mutations in the POLE and POLD1 genes may be associated with increased risk for CRC. In an analysis of 266 unrelated probands with polyposis or who met the Amsterdam criteria, a POLE mutation was found in 1.5% of patients. In an analysis of 858 Spanish patients with early-onset and/or familial CRC and/or colonic polyposis, only one patient was found to have a POLE mutation. Mutations in the CHEK2 and MSH3 genes may also be associated with increased risk for CRC. For CHEK2, the 1100delC and I157T variants were found in meta-analytic reviews to be associated with both unselected and familial CRC. Mutations in the protein-coding gene GALNT12 is also believed to be associated with increased risk for CRC. Heterozygous mutations in the ATM gene and heterozygous mutations in the DNA RECQL-helicase gene BLM may also increase risk for CRC. Mutations in the AXIN2 and NTHL1 genes are associated with polyposis and oligodontia. There are emerging data that RPS20 mutations may be associated with increased risk for CRC, but more data are required to strengthen this association.

Although research has demonstrated a potential risk for CRC associated with these mutations, the value of including these genes for clinical testing (eg, as part of a multi-gene panel) remains uncertain. Nonetheless, the panel recognizes that many testing companies offer panels that include these genes, and that patients are being tested and may need guidance regarding subsequent screening and surveillance.
Accordingly, while the panel recommends caution in recommending multi-gene testing, guidance on management of results is discussed below.

Evidence to support screening and surveillance is limited, but the panel has conditionally developed a framework of recommendations for genes commonly included in multi-gene panels (GENE-7). Screening recommendations for carriers of \textit{GREM1}, \textit{POLD1}, \textit{POLE}, \textit{AXIN2}, \textit{NTHL1} and/or \textit{MSH3} mutations are as follows (GENE-7): begin colonoscopy at age 25 to 30 years, and receive follow-up colonoscopies every 2 to 3 years if negative. If polyps are found, screen with colonoscopy every 1 to 2 years with consideration of surgery if the polyp burden becomes unmanageable by colonoscopy. Surgical evaluation should be provided if appropriate. The panel recognizes that data to support the surveillance recommendations for \textit{GREM}, \textit{POLD}, \textit{POLE}, \textit{AXIN2}, \textit{NTHL1}, and/or \textit{MSH3} mutations are currently evolving. Therefore, caution should be used when implementing final colonoscopy surveillance regimens in the context of patient preferences and new knowledge that may emerge.

As with the surveillance recommendations for \textit{GREM}, \textit{POLD}, \textit{POLE}, \textit{AXIN2}, \textit{NTHL1}, and \textit{MSH3} mutations, data to support the surveillance recommendations for \textit{APC} I1307K and \textit{CHEK2} mutations are also currently evolving. Therefore, the panel recommends caution when implementing final colonoscopy surveillance regimens in the context of patient preferences and new knowledge that may emerge. For carriers of \textit{APC} I1307K and \textit{CHEK2} mutations with CRC, the panel recommends colonoscopy surveillance based on the NCCN Guidelines for Colon Cancer and the NCCN Guidelines for Rectal Cancer. For carriers of \textit{APC} I1307K and \textit{CHEK2} mutations unaffected by CRC with a first-degree relative with CRC, the panel recommends colonoscopy screening every 5 years beginning at age 40 or 10 years prior to the first-degree relative’s age at CRC diagnosis (GENE-7). For carriers unaffected by CRC without a first-degree relative with CRC, the panel recommends colonoscopy screening every 5 years beginning at age 40 years (GENE-7).

Overall, as data regarding the clinical significance of genes associated with CRC risk emerge, the panel expects that these surveillance recommendations will evolve.


221. Yurgelun MB, Allen B, Kaldate RR, et al. Identification of a Variety of Mutations in Cancer Predisposition Genes in Patients With Suspected...


252. Rivera B, Perea J, Sanchez E, et al. A novel AXIN2 germline variant associated with attenuated FAP without signs of oligodontia or


APPENDIX 3
NCCN Guidelines® Insights
Genetic/Familial High-Risk Assessment: Colorectal, Version 3.2017
Featured Updates to the NCCN Guidelines

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Abstract
The NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal provide recommendations for the management of patients with high-risk syndromes associated with an increased risk of colorectal cancer (CRC). The NCCN Panel for Genetic/Familial High-Risk Assessment: Colorectal meets at least annually to assess comments from reviewers within their institutions, examine relevant data, and reevaluate and update their recommendations. These NCCN Guidelines Insights focus on genes newly associated with CRC risk on multigene panels, the associated evidence, and currently recommended management strategies.

From 1UC San Diego Moores Cancer Center; 2Duke Cancer Institute; 3University of Michigan Comprehensive Cancer Center; 4The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute; 5City of Hope Comprehensive Cancer Center; 6Fox Chase Cancer Center; 7Yale Cancer Center/Smilow Cancer Hospital; 8Massachusetts General Hospital Cancer Center; 9University of Colorado Cancer Center; 10Hereditary Colon Cancer Foundation; 11Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute; 12Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; 13Stanford Cancer Institute; 14The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; 15Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance; 16Robert H. Lurie Comprehensive Cancer Center of Northwestern University; 17The University of Texas MD Anderson Cancer Center; 18Moffitt Cancer Center; 19Mayo Clinic Cancer Center; 20Fred & Pamela Buffett Cancer Center; 21Memorial Sloan Kettering Cancer Center; 22Dana-Farber/Brigham and Women's Cancer Center; 23Vanderbilt-Ingram Cancer Center; 24Huntsman Cancer Institute at the University of Utah; 25University of Alabama at Birmingham Comprehensive Cancer Center; 26University of Wisconsin Carbone Cancer Center; and 27National Comprehensive Cancer Network.

*Provided content development and/or authorship assistance.

Please Note
The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. The NCCN Guidelines® Insights highlight important changes to the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the NCCN Guideline Panel discussion, including the literature reviewed.

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Release date: December 10, 2017; Expiration date: December 10, 2018

Learning Objectives:

Upon completion of this activity, participants will be able to:

• Integrate into professional practice the updates to the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal

• Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal

Disclosure of Relevant Financial Relationships

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Overview

Due to increased lifetime risks of multiple cancers associated with hereditary cancer syndromes, it is important to identify genes that may affect risk assessment and potential management strategies. In addition, early intervention has the potential to decrease cancer incidence and mortality in affected individuals. The recent introduction of multigene 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, multigene testing simultaneously analyzes a set of genes associated with a specific family cancer phenotype or multiple phenotypes, and may include syndrome-specific tests (ie, panels that test for only one syndrome, such as Lynch syndrome), cancer-specific tests (ie, panels that test for >1 gene associated with a specific type of cancer, such as colorectal cancer [CRC]), and comprehensive cancer panels (ie, panels that test for >1 gene associated with multiple cancers or cancer syndromes). The NCCN Guidelines...
Panel for Genetic/Familial High-Risk Assessment: Colorectal added information regarding multigene testing during the 2016 update.

Multigene testing could include high-risk genes associated with a specific cancer or both high- and moderate-risk genes. Comprehensive cancer risk panels, which include a large number of genes associated with a variety of cancer types, are also available. The basis for using multigene testing for patient care should be no different from the rationale for testing a single gene known to be associated with the development of a specific type of cancer. Testing is ideally focused on identifying a mutation known to be clinically actionable. Specifically, a clinically actionable mutation alters patient management when present. Multigene testing may be most useful when more than one gene can explain a patient’s clinical and family history. In these cases, multigene testing may be more efficient and/or cost-effective. Multigene testing may also be considered for those who tested negative for a particular syndrome but whose personal and family history is strongly suggestive of an inherited susceptibility.

Multigene testing is associated with several challenges. Most multigene panels include genes with limited data regarding degree of cancer risk among carriers and that support guidelines for risk management. In addition, the cancer risk of many of these genes is not clear when ascertained in individuals who do not have the typical phenotype historically associated with the cancer gene. Further, it is possible that the risks associated with these genes may not be due entirely to that gene only, but may also be influenced by gene/gene or gene/environment interactions. Multigene tests also increase the likelihood of detecting variants of uncertain significance (VUS), which range from 17% to 38%, with likelihood rates ranging from 6% to 10%. The considerable possibility of detecting a VUS adds to the complexity of counseling following multigene testing. Addressing these challenges will require large studies with adequate power to assess outcomes, yet such studies.

### TABLE 4: EVALUATION OF GENES COMMONLY INCLUDED ON MULTI-GENE PANELS

<table>
<thead>
<tr>
<th>GENE</th>
<th>STRENGTH OF EVIDENCE</th>
<th>RISK STATUS</th>
<th>ASSOCIATION</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>GREM1</td>
<td>Not well-established</td>
<td>Uncertain – presumed high risk from limited case reports</td>
<td>Hereditary mixed polyposis syndrome due to a 40kb duplication upstream of GREM1 in Ashkenazi Jewish ancestry only</td>
<td>Jaeger E, et al. Nat Genet 2012; 44:699-703.</td>
</tr>
<tr>
<td>MLH1</td>
<td>Well-established</td>
<td>High</td>
<td>Lynch syndrome</td>
<td>See Lynch Syndrome Guidelines (LS-1)</td>
</tr>
<tr>
<td>MSH2</td>
<td>Well-established</td>
<td>High</td>
<td>Lynch syndrome</td>
<td>See Lynch Syndrome Guidelines (LS-1)</td>
</tr>
<tr>
<td>MSH6</td>
<td>Well-established</td>
<td>High</td>
<td>Lynch syndrome</td>
<td>See Lynch Syndrome Guidelines (LS-1)</td>
</tr>
<tr>
<td>MUTYH biallelic mutations</td>
<td>Well-established</td>
<td>High</td>
<td>MUTYH-associated polyposis</td>
<td>See APC and MUTYH Genetic Testing Criteria (APC/MUTYH-1)</td>
</tr>
<tr>
<td>MUTYH heterozygotes</td>
<td>Not well-established</td>
<td>Uncertain – moderate at most</td>
<td>Possible increased risk for colorectal cancer</td>
<td>Win AK, et al. Gastroenterology 2014;146:1208-1211.</td>
</tr>
</tbody>
</table>

Continued on next page
**MULTI-GENE TESTING**

**TABLE 4: EVALUATION OF GENES COMMONLY INCLUDED ON MULTI-GENE PANELS**

<table>
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<th>GENE</th>
<th>STRENGTH OF EVIDENCE</th>
<th>RISK STATUS</th>
<th>ASSOCIATION</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMS2</td>
<td>Well-established</td>
<td>High</td>
<td>Lynch syndrome</td>
<td>See Lynch Syndrome Guidelines (LS-1)</td>
</tr>
<tr>
<td>PTEN</td>
<td>Well-established</td>
<td>Moderate-High</td>
<td>Cowden syndrome/PTEN Hamartoma syndrome</td>
<td>See NCCN Guideline Genetic Familial High-Risk Assessment: Breast and Ovarian</td>
</tr>
<tr>
<td>SMAD4</td>
<td>Well-established</td>
<td>High</td>
<td>Juvenile polyposis syndrome</td>
<td>See Juvenile Polyposis Syndrome Guidelines (JPS-1)</td>
</tr>
<tr>
<td>STK11</td>
<td>Well-established</td>
<td>High</td>
<td>Peutz-Jeghers syndrome</td>
<td>See Peutz-Jeghers Syndrome Syndrome Guidelines (PJS-1)</td>
</tr>
<tr>
<td>TP53</td>
<td>Well-established</td>
<td>High</td>
<td>Li Fraumeni syndrome</td>
<td>See NCCN Guideline Genetic Familial High-Risk Assessment: Breast and Ovarian</td>
</tr>
</tbody>
</table>

Continued on next page

**RS2O2** is an emerging gene that is potentially linked to CRC, and there are not enough data at present to include RPS20 on this list.

will be difficult to conduct given the low incidence of hereditary disease.

There are other issues to consider regarding multigene testing. First, commercially available tests may differ significantly on a number of factors, such as number of genes analyzed, turnaround time, and insurance coverage. Tests requiring a longer turnaround time may not be suitable for patients who need rapid results to inform surgical decision-making or other treatment choices. In addition, there is variation across commercial laboratory providers in the interpretation of genetic variants or mutations; therefore, the specific laboratory and multigene test should be chosen carefully. Second, in some cases, next-generation sequencing may miss some mutations that would have been detected with traditional single-gene analysis. Third, mutations identified for more than one gene add complexity that may lead to difficulty in making risk management recommendations. A management plan should only be developed for identified gene mutations that are clinically actionable; care should be taken to ensure that overtreatment or overscreening does not occur due to findings for which clinical management is uncertain, or findings that are incorrectly interpreted due to lack of evidence. This issue is particularly salient when the clinical management under consideration may include prophylactic surgery, such as colectomy.

Multigene testing is a new and rapidly growing field, but there is currently a lack of evidence regarding proper procedures and risk management strategies that should follow testing, especially when mutations are found for moderate-risk genes or when a VUS is found. For this reason, the NCCN panel recommends multigene testing be offered in the context of professional genetic expertise, with pretest and posttest counseling. Panel recommendations are in agreement with those by ASCO, which issued an updated statement regarding genetic testing in 2015. Carriers of a genetic mutation should be encouraged to participate in clinical trials or genetic registries.
### TABLE 5: RECOMMENDED MANAGEMENT FOR GENES THAT MAY CONFER A RISK FOR COLORECTAL CANCER

<table>
<thead>
<tr>
<th>GENE</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>See NCCN Guidelines for Familial Adenomatous Polyposis (FAP-1)</td>
</tr>
<tr>
<td>BMPR1A</td>
<td>See NCCN Guidelines for Juvenile Polyposis Syndrome (JPS-1)</td>
</tr>
<tr>
<td>LS syndrome genes (MLH1, MSH2, MSH6, PMS2, EPCAM)</td>
<td>See NCCN Guidelines for Lynch Syndrome (LS-2)</td>
</tr>
<tr>
<td>MUTYH biallelic mutations</td>
<td>See NCCN Guidelines for MUTYH-Associated Polyposis (MAP-1)</td>
</tr>
<tr>
<td>PTEN</td>
<td>See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian</td>
</tr>
<tr>
<td>STK11</td>
<td>See NCCN Guidelines for Peutz-Jeghers Syndrome (PJS-1)</td>
</tr>
<tr>
<td>SMAD4</td>
<td>See NCCN Guidelines for Juvenile Polyposis Syndrome (JPS-1)</td>
</tr>
<tr>
<td>TP53</td>
<td>See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian</td>
</tr>
<tr>
<td>GREM1</td>
<td></td>
</tr>
<tr>
<td>POLE</td>
<td></td>
</tr>
<tr>
<td>AXIN2</td>
<td></td>
</tr>
<tr>
<td>NTHL1</td>
<td></td>
</tr>
<tr>
<td>MSH3</td>
<td></td>
</tr>
</tbody>
</table>
| APC I1307K mutation | For probands with colorectal cancer and one of these mutations:  
  - See surveillance recommendations for post-colorectal cancer resection  
  - NCCN Guidelines for Colon Cancer  
  - NCCN Guidelines for Rectal Cancer  
  - Colonoscopy screening every 5 years, beginning at age 40 or 10 years prior to age of first-degree relative’s age at CRC diagnosis.  
  - For probands unaffected by colorectal cancer and no first-degree relative with colorectal cancer:  
    - Colonoscopy screening every 5 years, beginning at age 40. |
| CHEK2 | |
| MUTYH heterozygotes | For probands unaffected by colorectal cancer with a first-degree relative with colorectal cancer:  
  - Colonoscopy screening every 5 years, beginning at age 40 or 10 years prior to age of first-degree relative’s age at CRC diagnosis.  
  - For probands unaffected by colorectal cancer with NO family history of colorectal cancer:  
    - Data are uncertain if specialized screening is warranted. |

*The panel recognizes that data to support the surveillance recommendations for these particular genes are evolving at this time. Caution should be used when implementing final colonoscopy surveillance regimens in context of patient preferences and new knowledge that may emerge.

Multigene testing is not recommended when:
- There is an individual from a family with a known mutation and there is no other reason for multigene testing;
- The patient’s family history is strongly suggestive of a specific known hereditary syndrome for which single-gene analysis may provide definitive diagnosis; or,
- The patient is diagnosed with CRC with microsatellite instability (MSI) or loss of ≥1 DNA mismatch repair (MMR) proteins.

In these 3 scenarios, syndrome-specific panels may be considered.

Multigene testing may be considered in the following scenarios:
- A patient with a personal or family history that meets criteria for >1 hereditary cancer syndrome (eg, Lynch syndrome and BRCA-related breast and/or ovarian cancer)
- Colonic polyposis with uncertain histology
- Adenomatous or mixed polyposis (specific to APC, MUTYH, POLE, and POLD1)
- Family history does not meet criteria for established testing guidelines but there is suspicion of hereditary cancer, and an appropriate panel is available
- Family history is limited or unknown but patient has concerns about hereditary cancer
- As second-line testing when first-line testing (eg, syndrome-specific or single-gene) is inconclusive

However, additional indications for multigene testing may exist based on clinical judgment.

Risk for CRC and management of genes with well-established risk for CRC, including Lynch syndrome, familial adenomatous polyposis (FAP), and MUTYH-associated polyposis (MAP), have been reviewed in detail in prior NCCN Guidelines, and have been updated annually (to view the most recent and complete version of these guidelines, visit
NCCN.org). In the case of many genes newly associated with CRC, the evidence is still emerging. To establish the clinical utility of these genes, it is important to review the strength of the evidence.15 Previously, the panel conditionally developed a framework of recommendations for genes commonly included in multigene panels (see GENE-7; page 1470). During the 2017 guidelines update meeting, the panel evaluated the strength of the evidence based on published reports supporting these genes. These NCCN Guidelines Insights summarize data focused on genes newly associated with CRC risk and current recommended management strategies, although the panel notes that the link between mutations/alterations in some of these genes and increased CRC risk is incompletely defined due to limited evidence. These include mutations/alterations in the following genes: APC (I1307K polymorphism), AXIN2, CHEK2, GREM1, MSH3, MUTYH (monoallelic), NTHL1, POLE1, and POLE.

Genes Newly Associated With CRC Frequently Seen on Multigene Panels: Evidence and Management Approaches

APC I1307K Mutation
The adenomatous polyposis coli (APC) gene is a tumor-suppressor gene associated with CRC.16 There is well-established evidence that the I1307K polymorphism in the APC gene, which occurs in approximately 6% to 8% of individuals of Ashkenazi Jewish decent, predisposes carriers to CRC.17–21 In an analysis of 3,305 individuals from Israel who underwent colonoscopic examinations, 8% were identified as carriers of the I1307K polymorphism, and the overall adjusted odds ratio (OR) for colorectal neoplasia among carriers was 1.51 (95% CI, 1.16–1.98).17 A subgroup analysis found that the prevalence of the I1307K polymorphism in individuals of Ashkenazi Jewish decent was 10.1% and the adjusted OR was 1.75 (95% CI, 1.26–2.45).17 A meta-analysis including 40 studies showed that compared with carriers of wild-type I1307K, individuals of Ashkenazi Jewish decent who carried the I1307K polymorphism had a significantly increased risk of colorectal neoplasia, with a pooled OR of 2.17 (95% CI, 1.64–2.86).20 Some studies have identified the I1307K polymorphism in the APC gene in individuals of non–Ashkenazi Jewish and Arabic descent, although the prevalence is higher in individuals of Ashkenazi Jewish decent.22–24 An analysis of 900 cases from a population-based case-control study in northern Israel found the I1307K polymorphism in the APC gene in 78 CRC cases, with a prevalence of 11.2%, 2.7%, and 3.1% among individuals of Ashkenazi Jewish, non-Ashkenazi Jewish, and Arabic decent, respectively.23 Overall, however, evidence is insufficient to determine whether risk for CRC associated with the APC I1307K polymorphism differs among individuals with Ashkenazi decent versus without, and the panel recognizes that some individuals may not be aware of their Ashkenazi heritage.

For carriers of the APC I1307K mutation with CRC, the panel recommends colonoscopy surveillance based on NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colon Cancer and for Rectal Cancer (to view the most recent version of these guidelines, visit NCCN.org). For carriers of the APC I1307K mutation unaffected by CRC with a first-degree relative with CRC, the panel recommends colonoscopy surveillance every 5 years beginning at age 40 years or at 10 years younger than the first-degree relative’s age at CRC diagnosis (see GENE-7; page 1470). For carriers unaffected by CRC without a first-degree relative with CRC, the panel recommends colonoscopy screening every 5 years beginning at age 40 years (see GENE-7; page 1470).

AXIN2 Mutations
Mutations in the Axin-related protein (AXIN2) gene are associated with polyposis and oligodontia.25–29 In a study of a 4-generation family from Finland, 11 family members had oligodontia, 8 of whom had either CRC or precancerous lesions, attributed to a nonsense mutation in the AXIN2 gene.25 Other studies also support the association of AXIN2 mutations and oligodontia.27,29 A report described a family with a history of oligodontia and other findings, including colonic polyposis, gastric polyps, a mild ectodermal dysplasia phenotype, and early-onset CRC and breast cancer, in which an inherited AXIN2 mutation (c.1989G>A) segregated in an autosomal dominant pattern.27 Another study of 23 families with FAP resulted in the identification of a novel AXIN2 variant (c.1387C>T) in one family with attenuated FAP (AFAP).28 Carriers of the variant had a variable number of polyps but no oligodontia or ectodermal dysplasia.28 During the 2017 update, AXIN2 was added to a list of genes
A recent study suggests that the CHEK2-MSH3 gene is associated with increased risk of breast cancer and CRC. In a population-based study of 5,953 patients with breast, prostate, or colon cancers (1,934 patients with colon cancer), 533 were CHEK2-positive and 431 were affected relatives. After adjusting for mutation type, the risk of colon cancer was higher among relatives of probands with colon cancer than among relatives of patients with prostate or breast cancer (hazard ratio [HR], 4.2; 95% CI, 2.4–7.8; P=.0001). Significant associations between CHEK2 mutations and CRC risk have been identified in meta-analyses. One meta-analysis of 7 studies that included 4,029 cases and 13,844 controls based on search criteria found a significant association between the CHEK2 I157T variant and CRC risk. For carriers of CHEK2 mutations, the NCCN Panel recommends similar management strategies as described for carriers of the APC I1307K mutation.

**CHEK2 Mutations**
Germline mutations in the cell cycle checkpoint kinase 2 (CHEK2) gene are associated with increased risk of breast cancer and CRC. In a population-based study of 5,953 patients with breast, prostate, or colon cancers (1,934 patients with colon cancer), 533 were CHEK2-positive and 431 were affected relatives. After adjusting for mutation type, the risk of colon cancer was higher among relatives of probands with colon cancer than among relatives of patients with prostate or breast cancer (hazard ratio [HR], 4.2; 95% CI, 2.4–7.8; P=.0001). Significant associations between CHEK2 mutations and CRC risk have been identified in meta-analyses. One meta-analysis of 7 studies that included 4,029 cases and 13,844 controls based on search criteria found a significant association between the CHEK2 I157T variant and CRC risk. For carriers of CHEK2 mutations, the NCCN Panel recommends similar management strategies as described for carriers of the APC I1307K mutation.

**GREM1 Alterations**
Hereditary mixed polyposis syndrome (HMPS) is a rare autosomal dominant condition that occurs primarily in individuals of Ashkenazi Jewish descent and is characterized by multiple types of colorectal polyps, extracolonic tumors, onset of polyps in adolescence, and progression of some polyps to advanced adenomas. HMPS is due to a 40-kb duplication upstream of the gremlin 1 gene (GREM1), which increases ectopic GREM1 expression in normal epithelium. Exome sequencing combined with linkage analyses and detection of copy-number variations identified a 16-kb duplication upstream of GREM1 in a family of non–Ashkenazi Jewish descent with AFAP. For carriers of GREM1 alterations, the panel recommends similar management strategies as described for carriers of AXIN2 mutations (see GENE-7; page 1470).

**MSH3 Mutations**
MutS homolog 3 (MSH3) is a DNA MMR gene implicated in tumorigenesis of colon cancer with MSI. Recent data have suggested that biallelic MSH3 germline mutations are a recessive subtype of colorectal adenomatous polyposis. During the 2017 NCCN Guidelines update, MSH3 was added to a list of genes commonly included on multigene panels (see GENE-5; page 1468). However, given available data, the panel agreed that the strength of evidence linking MSH3 to increased CRC risk is not currently well established. For carriers of 2 MSH3 mutations, the panel recommends similar management strategies as described for carriers of AXIN2 mutations (see GENE-7; page 1470).

**MUTYH (Monoallelic) Mutations**
MUTYH is a base excision repair gene involved in repairing oxidative DNA damage. Individuals with a germline mutation in one allele of the MUTYH gene are thought to have a modest or slightly increased risk of CRC. A recent study suggests that the risks may be higher than previously estimated. This study analyzed 2,332 individuals with monoallelic MUTYH mutations among 9,504 relatives of 264 CRC cases with a MUTYH mutation. The estimated CRC risks, up to 70 years of age, were 7.2% for male carriers of monoallelic MUTYH mutations (95% CI, 4.6%–11.3%) and 5.6% for female carriers (95% CI, 3.6%–8.8%), irrespective of family history. The risks for CRC were higher for carriers of monoallelic MUTYH mutations with a first-degree relative with CRC. Another study evaluated the frequency of monoallelic MUTYH mutations and colorectal adenomas, and found that 13 of 72 individuals with CRC were monoallelic MUTYH mutation carriers, and 11 of the 13 had a family history of cancer in first- or second-degree relatives.

During the 2017 update, the NCCN Panel revised management recommendations for monoallelic MUTYH mutation carriers based on the data and expert consensus (see GENE-7; page 1470). For probands unaffected by CRC with a first-degree relative with CRC, the panel recommends colonoscopy surveillance every 5 years, beginning at age 40 years or at 10 years younger than the age of the first-degree
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relative's age at CRC diagnosis. For probands unaffected by CRC without a first-degree relative with CRC, the panel notes that the data are not well established and it is uncertain whether specialized screening is warranted.

**NTHL1 Mutations**
The endonuclease III–like 1 (NTHL1) gene is involved in base excision repair and acts on oxidized pyrimidine residues. A recent study suggests a role for NTHL1 mutations in colorectal polyposis. Whole-exome sequencing on 51 individuals from 48 families diagnosed with polyposis identified a homozygous germline nonsense mutation in NTHL1 in 7 affected individuals from 3 unrelated families. During the 2017 update, NTHL1 was added to a list of genes commonly included on multigene panels (see GENE-6; page 1469). For carriers of 2 NTHL1 mutations, the panel recommends similar management strategies as described for carriers of AXIN2 mutations (see GENE-7; page 1470).

**POLD1 and POLE Mutations**
DNA polymerases delta [8] (POLD1) and epsilon [e] (POLE) are involved in DNA proofreading and replication. Mutations in the POLD1 and POLE genes may be associated with polyposis and an increased risk for CRC. Using whole-genome sequencing in combination with linkage and association analysis, heterozygous POLD1 and POLE germline variants were identified in multiple adenoma and/or CRC cases. In an analysis of 858 Spanish patients with early-onset and/or familial CRC and/or colonic polyposis, only 1 patient was found to have a POLE mutation. In an analysis of 266 unrelated probands with polyposis or who met the Amsterdam criteria, a POLE mutation was found in 1.5% of patients. Novel variants for both POLD1 and POLE have been identified in individuals with CRC, broadening the phenotypic spectrum of POLD1- and POLE-associated polyposis. Presently, for carriers of POLD1 and POLE mutations, the panel recommends similar management strategies as described for carriers of AXIN2 mutations (see GENE-7; page 1470).

**Summary and Conclusions**
During the panel meeting for the 2017 update, panel members discussed a number of important updates to the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, including the strength of evidence linking mutations in genes newly associated with CRC risk and management recommendations for these genes. These include mutations/alterations in APC (I1307K polymorphism), AXIN2, CHEK2, GREM1 (upstream duplications), MSH3, MUTYH (monoallelic), NTHL1, POLD1, and POLE. Although research has demonstrated a potential risk for CRC associated with mutations in these genes, the value of including these genes for clinical testing (eg, as part of a multigene panel) remains uncertain. The panel urges caution in implementing routine clinical testing for genes for which the cancer risk and management strategies are currently uncertain, and some panel members have concerns about the observed practice of genetic testing companies regularly expanding the list of tested genes despite availability of only weak evidence to support cancer risk. Nonetheless, the panel recognizes that many testing companies offer panels that include these genes, and that patients are being tested and may need guidance regarding subsequent screening and surveillance. As additional data regarding the clinical significance of genes associated with CRC risk emerge, the NCCN Panel expects that these surveillance recommendations will continue to evolve.

**References**
Genetic/Familial High-Risk Assessment: Colorectal, Version 3.2017

Posttest Questions

1. According to the 2017 NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, the following genes newly associated with CRC frequently seen on multigene panels may be associated with an increased risk of CRC:
   a. MSH3
   b. MSH2
   c. CHEK2
   d. a and b
   e. a, b, and c
   f. a and c

2. True or False: An individual from a family with a known mutation and no other reason for multigene testing is an appropriate rationale for considering multigene testing.

3. According to the 2017 NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, when should an individual with monoallelic MUTYH mutations unaffected by CRC and with a first-degree relative with CRC consider colonoscopy surveillance?
   a. 50 years of age or at 10 years younger than the age of first-degree relative's age at CRC diagnosis
   b. 40 years of age or at 10 years younger than the age of first-degree relative's age at CRC diagnosis
   c. 40 years of age or at 5 years younger than the age of first-degree relative's age at CRC diagnosis
   d. 50 years of age or at 5 years younger than the age of first-degree relative's age at CRC diagnosis
   e. Data are unclear whether specialized screening is needed