

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.

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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

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TABLE 4: EVALUATION OF CRC GENES COMMONLY INCLUDED ON MULTI-GENE PANELS^c

GENE	STRENGTH OF EVIDENCE	RISK LEVEL	ASSOCIATION	REFERENCE
<i>APC</i>	Well-established	High	Familial adenomatous polyposis (FAP) & Attenuated FAP	See <i>APC</i> and <i>MUTYH</i> Genetic Testing Criteria (<i>APC/MUTYH-1</i>)
<i>APC</i> I1307K mutation	Well-established	Moderate	Increased frequency in Ashkenazi Jewish individuals; increased risk for colorectal cancer	Boursi B, et al. <i>Eur J Cancer</i> 2013;49:3680-3685. Liang J, et al. <i>Am J Epidemiol</i> 2013;177:1169-1179.
<i>ATM</i>	Not well-established	Unclear – moderate at most	Increased risk for breast cancer and colorectal cancer	Thompson D, et al. <i>J Natl Cancer Inst</i> 2005;97:813-822. Olsen JH, et al. <i>Br J Cancer</i> 2005;93:260-265.
<i>AXIN2</i>	Not well-established	Uncertain – presumed high risk from limited case reports	Polyposis and oligodontia	Lammi L, et al. <i>Am J Hum Genet</i> 2004;74:1043-50. Marvin ML, et al. <i>Am J Med Genet A</i> 2011;155A:898-902. Rivera B, et al. <i>Eur J Hum Genet</i> 2014;22:423-6. Lejuene S, et al. <i>Hum Mutat</i> 2006;27:1064. Wong S, et al. <i>Arch Oral Biol</i> 2014;59:349-53.
<i>BLM</i> heterozygotes	Not well-established	Uncertain – none to low	Possible increased risk for colorectal cancer	Cleary et al. <i>Cancer Res</i> 2003;3:1769-71. Baris et al. <i>Isr Med Assoc J</i> 2007;9:847-50. Laitman Y, et al. <i>Cancer Genet</i> . 2016;209:70-4.
<i>BMPR1A</i>	Well-established	High	Juvenile polyposis syndrome	See Juvenile Polyposis Syndrome Guidelines (<i>JPS-1</i>)
<i>CHEK2</i>	Not well-established	Moderate	Increased risk for breast, colon, and other cancers	Xiang HP, et al. <i>Eur J Cancer</i> 2011;47:2546-2551. Liu C, et al. <i>Asian Pac J Cancer Prev</i> 2012;13:2051-2055. Gronwald J, et al. <i>Br J Cancer</i> 2009;100:1508-1512.
<i>EPCAM</i>	Well-established	High	Lynch syndrome	See Lynch Syndrome Guidelines (<i>LS-1</i>)

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

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GENE-4

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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

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.¹ In addition, early intervention has the potential to decrease cancer incidence and mortality in affected individuals.^{2,3} 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

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MULTI-GENE TESTING

TABLE 4: EVALUATION OF GENES COMMONLY INCLUDED ON MULTI-GENE PANELS^c (CONTINUED)

GENE	STRENGTH OF EVIDENCE	RISK STATUS	ASSOCIATION	REFERENCE
<i>GALNT12</i>	Not well-established	Uncertain – moderate at most	Increased risk for colorectal cancer	Guda K, et al. Proc Natl Acad Sci U.S.A. 2009;106:12921-12925. Clarke E, et al. Hum Mutat 2012;33:1056-1058. Segui N, et al. Hum Mutat 2014;35:50-52.
<i>GREM1</i>	Not well-established	Uncertain – presumed high risk from limited case reports	Hereditary mixed polyposis syndrome due to a 40kb duplication upstream of <i>GREM1</i> in Ashkenazi Jewish ancestry only	Jaeger E, et al. Nat Genet 2012; 44:699-703.
<i>MLH1</i>	Well-established	High	Lynch syndrome	See Lynch Syndrome Guidelines (LS-1)
<i>MSH2</i>	Well-established	High	Lynch syndrome	
<i>MSH6</i>	Well-established	High	Lynch syndrome	
<i>MSH3</i>	Not well-established	Uncertain – presumed high risk from limited case reports	Polyposis	Adam R, et al. Am J Hum Genet. 2016;99:337-51.
<i>MUTYH</i> biallelic mutations	Well-established	High	<i>MUTYH</i> -associated polyposis	See <i>APC</i> and <i>MUTYH</i> Genetic Testing Criteria (<i>APC/MUTYH-1</i>)
<i>MUTYH</i> heterozygotes	Not well-established	Uncertain – moderate at most	Possible increased risk for colorectal cancer	Win AK, et al. Gastroenterology 2014;146:1208-1211.

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GENE-5

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.⁴ 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.⁴ 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.^{4,5}

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.^{4,6-9} 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.⁴ 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 unknown/uncertain significance (VUS),^{4,5,8-12} with likelihood rates ranging from 17% to 38%.^{6,8,10,13} 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

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MULTI-GENE TESTING

TABLE 4: EVALUATION OF GENES COMMONLY INCLUDED ON MULTI-GENE PANELS^c (CONTINUED)

GENE	STRENGTH OF EVIDENCE	RISK STATUS	ASSOCIATION	REFERENCE
<i>NTHL1</i>	Not well-established	Uncertain – presumed high risk from limited case reports	Polyposis	Weren RD, et al. <i>Nat Genet</i> 2015;47:668-671. Rivera B, et al. <i>N Engl J Med</i> 2015;373:1985–1986. Broderick P, et al. <i>BMC Cancer</i> 2006;6:243.
<i>POLD1</i>	Not well-established	Uncertain – presumed high risk from limited case reports	Polymerase proofreading-associated polyposis	Palles C, et al. <i>Nat Genet</i> 2015; 45:136-144. Spier I, et al. <i>Int J Cancer</i> 2015;137:320-331. Bellido F, et al. <i>Genet Med</i> 2017;18:325-332.
<i>POLE</i>	Not well-established	Uncertain – presumed high risk from limited case reports	Polymerase proofreading-associated polyposis	Bellido F, et al. <i>Genet Med</i> 2017;18:325-332.
<i>PMS2</i>	Well-established	High	Lynch syndrome	See Lynch Syndrome Guidelines (LS-1)
<i>PTEN</i>	Well-established	Moderate-High	Cowden syndrome/ PTEN Hamartoma syndrome	See NCCN Guideline Genetic Familial High-Risk Assessment: Breast and Ovarian
<i>SMAD4</i>	Well-established	High	Juvenile polyposis syndrome	See Juvenile Polyposis Syndrome Guidelines (JPS-1)
<i>STK11</i>	Well-established	High	Peutz-Jeghers syndrome	See Peutz-Jegher syndrome Syndrome Guidelines (PJS-1)
<i>TP53</i>	Well-established	High	Li Fraumeni syndrome	See NCCN Guideline Genetic Familial High-Risk Assessment: Breast and Ovarian

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

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GENE-6

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.⁴ Second, in some cases, next-generation sequencing may miss some mutations that would have been detected with traditional single-gene analysis.⁴ Third, mutations identified for more than one gene add complexity that may lead to difficulty in making risk management recommendations.⁵ 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 2015.¹⁴ Carriers of a genetic mutation should be encouraged to participate in clinical trials or genetic registries.

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MULTI-GENE TESTING
TABLE 5: RECOMMENDED MANAGEMENT FOR GENES THAT MAY CONFER A RISK FOR COLORECTAL CANCER

GENE	RECOMMENDATION
<i>APC</i>	See NCCN Guidelines for Familial Adenomatous Polyposis (FAP-1)
<i>BMPR1A</i>	See NCCN Guidelines for Juvenile Polyposis Syndrome (JPS-1)
LS syndrome genes (<i>MLH1, MSH2, MSH6, PMS2, EPCAM</i>)	See NCCN Guidelines for Lynch Syndrome (LS-2)
<i>MUTYH</i> biallelic mutations	See NCCN Guidelines for <i>MUTYH</i> -Associated Polyposis (MAP-1)
<i>PTEN</i>	See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian
<i>STK11</i>	See NCCN Guidelines for Peutz-Jeghers Syndrome (PJS-1)
<i>SMAD4</i>	See NCCN Guidelines for Juvenile Polyposis Syndrome (JPS-1)
<i>TP53</i>	See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian
<i>GREM1</i> ^d	<ul style="list-style-type: none"> • Begin colonoscopy at age 25–30 and every 2–3 y if negative. If polyps are found, colonoscopy every 1–2 y with consideration of surgery if the polyp burden becomes unmanageable by colonoscopy. • Surgical evaluation if appropriate.
<i>POLD1</i> ^d	
<i>POLE</i> ^d	
<i>AXIN2</i>	
<i>NTHL1</i>	
<i>MSH3</i>	
<i>APC</i> I1307K mutation ^d <i>CHEK2</i> ^d	
<i>MUTYH</i> heterozygotes ^d	<ul style="list-style-type: none"> • For probands unaffected by colorectal cancer with a first-degree relative with colorectal cancer: <ul style="list-style-type: none"> ▶ Colonoscopy screening every 5 years, beginning at age 40 y 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: <ul style="list-style-type: none"> ▶ Data are uncertain if specialized screening is warranted.

^dThe 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.

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GENE-7

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

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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*, *POLD1*, 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 descent, 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 descent 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 descent 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 descent.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 descent, respectively.²³ Overall, however, evidence is insufficient to determine whether risk for CRC associated with the *APC* I1307K polymorphism differs among individuals with Ashkenazi descent 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

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commonly included on multigene panels (see GENE-4; page 1467). For carriers of *AXIN2* mutations, the panel recommends initiation of colonoscopic surveillance at age 25 to 30 years, and if no polyps are located, a repeat colonoscopy every 2 to 3 years. If polyps are found, colonoscopic surveillance every 1 to 2 years is recommended, with consideration of surgical interventions if the polyp burden becomes unmanageable by colonoscopy (see GENE-7; page 1470).

CHEK2 Mutations

Germline mutations in the cell cycle checkpoint kinase 2 (*CHEK2*) gene are associated with increased risk of breast cancer and CRC.^{30–32} 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.³⁰ 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; $P=.0001$).³⁰ Significant associations between *CHEK2* mutations and CRC risk have been identified in meta-analyses.^{31,32} 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.³¹ 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.^{33,34} HMPS is due to a 40-kb duplication upstream of the gremlin 1 gene (*GREM1*), which increases ectopic *GREM1* expression in normal epithelium.³³ 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.³⁵ For carriers of *GREM1* alterations, the panel recommends similar management strategies as de-

scribed 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.³⁶ Recent data have suggested that biallelic *MSH3* germline mutations are a recessive subtype of colorectal adenomatous polyposis.³⁷ 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.^{38–40} A recent study suggests that the risks may be higher than previously estimated.⁴¹ 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.⁴¹ The risks for CRC were higher for carriers of monoallelic *MUTYH* mutations with a first-degree relative with CRC.⁴¹ 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.⁴²

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.⁴³ A recent study suggests a role for *NTHL1* mutations in colorectal polyposis.⁴⁴ 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.⁴⁴ 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 [δ]1 (*POLD1*) and epsilon [ϵ] (*POLE*) are involved in DNA proofreading and replication.⁴⁵ Mutations in the *POLD1* and *POLE* genes may be associated with polyposis and an increased risk for CRC.^{46–49} 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.⁴⁷ 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.⁴⁸ 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.⁵⁰ Novel variants for both *POLD1* and *POLE* have been identified in individuals with CRC,

broadening the phenotypic spectrum of *POLD1*- and *POLE*-associated polyposis.^{46,51} 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.

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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

