



Familial polyposis gene testing

Clinical Policy ID: CCP.1050

Recent review date: 11/2023

Next review date: 3/2025

Policy contains: Familial polyposis gene testing; familial adenomatous polyposis; genetic testing; Lynch syndrome; MutY homologue-associated polyposis.

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Coverage policy

Familial polyposis gene testing is clinically proven and, therefore, may be medically necessary for any of the following indications (National Comprehensive Cancer Network, 2023):

- For members who have a personal or family history, regardless of degree of relatedness of the family member, of a pathogenic variant known to be associated with a colorectal polyposis or cancer gene.
- For members who have a personal history of any of the following:
 - At least 11 adenomatous colonic polyps.
 - At least two hamartomatous polyps.
 - At least five serrated polyps proximal to the sigmoid colon.
- A family member before age 50 diagnosed with colorectal cancer related to Lynch syndrome.
- More than one family member diagnosed with colorectal cancer related to Lynch syndrome at any age.
- For members with no personal history of a suspicious polyposis syndrome but who have a personal or family history indicating an increased risk for a hereditary cancer syndrome, e.g., Lynch syndrome-related

cancers, retinal pigment epithelium, osteomas, supernumerary teeth, desmoid tumor, cribriform variant of papillary thyroid cancer, brain cancer (usually medulloblastoma), and hepatoblastoma.

See related policies:

- CCP.1319 Colorectal cancer screening.
- CCP.1235 Genetic testing for hereditary cancer susceptibility.
- CCP.1468 Molecular analysis for targeted therapy for colorectal cancer.

Limitations

Germline testing for hereditary colorectal cancer syndromes is limited to one test per lifetime. Non-duplicative testing may be medically necessary to identify different genetic content. Providers will be expected to provide a rationale for additional testing.

Genetic testing provided by commercial entities that offer ancestry or health information through microarray-based single nucleotide polymorphism testing is investigational/not clinically proven and, therefore, not medically necessary, as this testing has not been validated for clinical use (National Comprehensive Cancer Network, 2023).

MutY homologue mutation testing for members of a polyposis family with a clear autosomal dominant inheritance pattern is investigational/not clinically proven and, therefore, not medically necessary, because its clinical utility has not been established (National Comprehensive Cancer Network, 2023).

Alternative covered services

- Genetic counseling.
- Guideline-directed colon cancer surveillance as preventive services.
- Guideline-directed treatment.

Background

Lynch syndrome, familial adenomatous polyposis, and MutY homologue-associated polyposis, the three known types of inherited colorectal cancer, account for up to 5% of all colon cancers (Hegde, 2014). Lynch syndrome is caused by a single dominant mutation inherited in the germline and is the most common inherited type. MutY homologue-associated polyposis is an autosomal recessive hereditary syndrome that predisposes individuals to attenuated polyposis and colorectal cancer.

Familial adenomatous polyposis is caused by a germline mutation in the adenomatous polyposis coli, characterized by the development of hundreds to thousands of precancerous colonic polyps. By age 35, 95% of individuals with the classic form of familial adenomatous polyposis have polyps, and the mean age of colon cancer diagnosis in untreated individuals is 39 years. Extracolonic manifestations are variably present and include polyps of the gastric fundus and duodenum, osteomas, dental anomalies, congenital hypertrophy of the retinal pigment epithelium, soft tissue tumors, desmoid tumors, and associated cancers (Yen, 2022).

Classical familial adenomatous polyposis has three types: attenuated familial adenomatous polyposis, Gardner syndrome, and Turcot syndrome. Attenuated familial adenomatous polyposis is a less severe form in which polyp growth is delayed and the condition is defined by the presence of an average of 30 polyps; the mean age of diagnosis is 55 years (U.S. National Institutes of Health, 2020). Lifetime risk of colorectal cancer in attenuated familial adenomatous polyposis is 70% (Lodewijk, 2015).

The diagnosis of adenomatous polyposis coli-associated polyposis conditions relies primarily on family history and clinical findings (e.g., Amsterdam Criteria and revised Bethesda Guidelines). Prediction models, tumor

testing, germline testing, and universal testing (i.e., testing all colorectal cancer for Lynch syndrome) may also be used to identify patients and family members at risk for such conditions.

Risk prediction models have been developed to avoid resource utilization in low-risk individuals. A threshold of greater than 5% predicted probability of carrying a Lynch syndrome mutation should prompt germline genetic testing. In patients who are at high risk for Lynch syndrome (e.g., meeting Amsterdam Criteria or a first-degree relative with a known Lynch syndrome mutation) or if tumor tissue from an affected relative is available, risk prediction models are not necessary before proceeding to germline testing (Rubenstein, 2015).

Molecular genetic testing is most often used in the early diagnosis of at-risk family members, as well as in confirming the diagnosis of familial adenomatous polyposis or attenuated familial adenomatous polyposis in individuals with equivocal findings (e.g., fewer than 100 adenomatous polyps). Options for genetic testing most often include single-gene testing using sequencing and deletion/duplication analysis and multi-gene panels (Yen, 2022).

The U.S. Food and Drug Administration (2023) has approved one nucleic acid-based companion diagnostic test for the colorectal cancer predisposition risk assessment. The 23andMe® Personal Genome Service® (PGS) Risk Report for MUTYH-Associated Polyposis (MAP) (23andMe Inc., Mountain View, California) is an over-the-counter test that uses qualitative genotyping to detect the Y179C and the G396D variants in the MutY homolog gene in genomic deoxyribonucleic acid isolated from human saliva collected from individuals 18 years or older. These two variants are the most common and best studied in people of Northern European descent and may not represent the majority of the MutY homolog variants in people of other ethnicities.

Findings

The Appendix lists validated genes for assessment of familial predisposition to colorectal cancer and polyposis using single gene tests or multigene panels. Validated genetic testing should be performed in a Clinical Laboratory Improvement Amendments-approved laboratory and informed by genetic counseling, where available.

Systematic reviews and evidence-based guidelines have identified several genetic mutations to aid in risk assessment and diagnosis of inherited colorectal cancer syndromes. Several organizations have developed recommendations for rational use of genetic testing for colorectal cancer predisposition: the American Gastroenterological Association (Rubenstein, 2015); the American Society of Clinical Oncology (Stoffel, 2015); and the American College of Gastroenterology (Syngal, 2015). The guidelines published by the American College of Medical Genetics and Genomics in 2014 note that while familial adenomatous polyposis can be diagnosed by colonoscopy, genetic testing is recommended to inform relatives of any risk (Hegde, 2014).

Genetic testing should be conducted in the context of pre- and post-test genetic counseling to ensure the patient's informed decision-making. When used appropriately, genetic testing can:

- Confirm the diagnosis of Lynch syndrome in a patient and/or family member.
- Determine the risk status of family members in pedigrees where the pathogenic mutation has been found.
- Justify surveillance of at-risk persons.
- Decrease the cost of surveillance by risk stratification.
- Aid decisions concerning family and career planning.

There is uniform agreement among guidelines that all patients with colorectal cancers should undergo genetic testing to confirm a diagnosis of suspected Lynch syndrome (Rubenstein, 2015; Stoffel, 2015; Syngal, 2015). Tumor testing using immunohistochemistry is performed to detect the presence or absence of proteins (MLH1, MSH2, MSH6, or PMS2) responsible for deoxyribonucleic acid mismatch repair. Germline testing is established

for detecting gene mutations in the mismatch repair pathway or loss of expression of the MSH2 gene that result in loss of mismatch repair protein expression (Rubenstein, 2015; Syngal, 2015). Deoxyribonucleic acid sequencing and large rearrangement analysis are the preferred molecular testing methods (Stoffel, 2015).

In the absence of a detected colorectal cancer or other cancer, the guidelines recommend the following for genetic testing for colorectal cancer predisposition:

- For patients who have a personal history of a tumor showing evidence of mismatch repair deficiency (and no demonstrated BRAF mutation or hypermethylation of MLH1), a known family mutation associated with Lynch syndrome, or a risk of $\geq 5\%$ chance of Lynch syndrome based on risk prediction models, genetic testing for Lynch syndrome is recommended (Syngal, 2015). Genetic testing should include germline mutation testing for the MLH1, MSH2, MSH6, PMS2, and/or EPCAM genes, or the altered gene(s) indicated by immunohistochemistry.
- Patients who have a personal history of more than 10 cumulative colorectal adenomas, a family history of one of the adenomatous polyposis syndromes, or a history of adenomas and familial adenomatous polyposis-type extracolonic manifestations (duodenal/ampullary adenomas, desmoid tumors [abdominal > peripheral], papillary thyroid cancer, congenital hypertrophy of the retinal pigment epithelium, epidermal cysts, osteomas) should undergo assessment for the adenomatous polyposis syndromes (Stoffel, 2015; Syngal, 2015). These should include:
 - APC and MutY homolog gene mutation analysis for patients with suspected adenomatous polyposis syndromes.
 - STK11 mutation analysis for patients with possible Peutz–Jeghers syndrome.
 - SMAD4 and BMPR1A mutation analysis for patients with possible Juvenile polyposis.
- For serrated polyposis syndrome, genetic testing is not routinely recommended, but MutY homolog mutation analysis may be considered in the presence of concurrent adenomas and/or a family history of adenomas.

A large meta-analysis assessed the association between genetic mutations and the risk of colorectal cancer identified a nominally statistically significant link ($P < .05$), for 62 variants in 50 candidate genes. An association considered strong was found for eight variants in five genes; moderate for two variants in two genes; weak for 52 variants in 45 genes, and nonexistent for 40 variants in 33 genes. Authors conclude these variants could explain 5% of familial colorectal cancer risk (Ma, 2014).

A systematic review of 11 studies compared 863 familial colorectal cancer cases, all diagnosed under the age of 55, and 1,604 individuals without colorectal cancer. Testing for nine gene mutations (NTHL1, RPS20, FANCM, FAN1, TP53, BUB1, BUB3, LRP6, and PTPN12) thought to increase colorectal cancer risk revealed only two mutations (NTHL1 and RPS20) present in the diagnosed cases, and no mutations detected among controls. The authors called for robust, well powered studies using whole exome sequencing to establish clinically actionable genes and mitigate against erroneous findings (Broderick, 2017).

A meta-analysis of 24 studies ($n = 2,025$) reviewed adenomatous polyposis coli promoter hypermethylation in colorectal cancer. Hypermethylation was elevated in colorectal adenoma versus normal colorectal tissue ($P < .0001$). The authors concluded hypermethylation is an early event in colorectal cancer, and a potentially valuable diagnostic marker in the early stage of the disease. However, hypermethylation is not significantly associated with survival in colorectal cancer patients (Liang, 2017).

Disparities may exist in risk factors for colorectal cancer, including in diagnosis of Lynch syndrome and familial adenomatous polyposis. African Americans have higher morbidity and mortality from these disorders than do other racial and ethnic groups, and are also less likely to transmit person/family history, creating an opportunity to improve this disparity and reduce gaps in outcomes with earlier screenings (Carethers, 2015).

In August 2018, we added one guideline/other and three peer-reviewed references to the policy, and removed four guidelines and other non-peer reviewed references. The policy ID changed from 02.01.08 to CCP.1050.

In 2019, we added one guideline/other to the policy, and updated a second guideline. The coverage policy was revised to be consistent with revised screening guidelines for high-risk colon cancer syndromes published by the National Comprehensive Cancer Network (2019).

In 2020, we updated the National Comprehensive Cancer Network (2020, update of 2019) guidelines and removed several older references from the policy. We added a table of validated genes commonly included in multi-gene panels that confer an increased risk for colorectal cancer and provide clinically actionable information for assessment of familial predisposition to colorectal cancer (see Appendix).

In 2021, we added new information based on updated National Comprehensive Cancer Network (2021) guidance:

- A new testing indication for members without a suspected polyposis syndrome but with a personal or family history indicating an increased risk for a hereditary cancer syndrome.
- A statement in the limitations section regarding genetic testing provided by commercial entities that offer ancestry or health information.

In 2022, the policy references were updated. No changes to coverage were warranted.

In 2023, we updated the references and identified no newly published relevant information to add to the policy. No policy changes were warranted.

References

On November 7, 2023, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “genetic testing,” familial polyposis,” and “colon cancer.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

8/2013: initial review date and clinical policy effective date: 12/2013

8/2014: Policy references updated.

8/2015: Policy references updated.

8/2016: Policy references updated.

8/2017: Policy references updated.

8/2018: Policy references updated. Policy ID changed.

9/2019: Policy references updated. Coverage revised.

11/2020: Policy references updated. Coverage includes testing information. Appendix added.

11/2021: Policy references updated. Coverage modified.

11/2022: Policy references updated.

11/2023: Policy references updated.

Appendix

Table 1. Validated genes for assessment of familial predisposition to colorectal cancer

Associated condition

Gene

Attenuated familial adenomatous polyposis	APC
Ashkenazi Jewish individuals	APC I1307K
Familial adenomatous polyposis	APC
Juvenile polyposis syndrome	BMPR1A, SMAD4
Lynch syndrome	EPCAM, MLH1, MSH2, MSH6, PMS2, BRAF, MUC16
MUTYH-associated polyposis	MUTYH
Peutz-Jeghers syndrome	STK11
Cowden syndrome/PTEN hamartoma syndrome	PTEN
Li-Fraumeni syndrome	TP53
Source: National Comprehensive Cancer Network (2023).	