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(See policy history boxes for previous effective dates)

Title: Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Description/Background

HEREDITARY COLORECTAL CANCERS

Currently, two types of hereditary colorectal cancers are well-defined; familial adenomatous polyposis (FAP) and Lynch syndrome (formerly hereditary non-polyposis colorectal cancer [CRC]). Lynch syndrome has been implicated in some endometrial cancers as well.

Familial Adenomatous Polyposis and Associated Variants

Familial Adenomatous Polyposis typically develops by age 16 years and can be identified by the appearance of hundreds to thousands of characteristics, precancerous colon polyps. If left untreated, all affected individuals will go on to develop CRC. Mean age of colon cancer diagnosis in untreated individuals is 39 years. FAP accounts for about 1% of CRC and may also be associated with osteomas of the jaw, skull, and limbs; sebaceous cysts; and pigmented spots on the retina referred to as congenital hypertrophy of the retinal pigment epithelium. FAP associated with these collective extraintestinal manifestations is sometimes referred to as Gardner syndrome. FAP may also be associated with central nervous system (CNS) tumors, referred to as Turcot syndrome.

Germline variants in the adenomatous polyposis coli (*APC*) gene, located on chromosome 5, are responsible for FAP and are inherited in an autosomal dominant manner. Variants in the *APC* gene result in altered protein length in about 80% to 85% of cases of FAP. A specific *APC* gene variant (I1307K) has been found in subjects of Ashkenazi Jewish descent, which may explain a portion of the familial colorectal cancer occurring in this population.

A subset of FAP patients may have an attenuated form of FAP, typically characterized by fewer than 100 cumulative colorectal adenomas occurs later in life at an average age of 50-55 years, but lifetime risk of CRC remains high (about 70% by age 80 years). The risk of extra-intestinal cancer is also lower but cumulative lifetime risk remains high (about 38%) compared with the general population.(1) Only 30% or fewer of attenuated FAP patients have APC variants; some of these patients have variants in the *MUTYH* (formerly *MYH*) gene and this form of the condition is called *MUTYH*-associated polyposis (MAP). MAP occurs with a frequency approximately equal to FAP, with some variability among prevalence estimates for both. While clinical features of MAP are similar to FAP or attenuated FAP, a strong multigenerational family history of polyposis is absent. Biallelic *MUTYH* variants are associated with a cumulative colorectal cancer risk of about 80% by age 70, whereas monoallelic *MUTYH* variant-associated risk of colorectal cancer appears to be relatively minimal, although still under debate.(2) Thus, inheritance for high-risk colorectal cancer predisposition is autosomal recessive in contrast to FAP. When relatively few (i.e., between 10 and 99) adenomas are present and family history is unavailable, the differential diagnosis may include both MAP and Lynch syndrome; genetic testing in this situation could include *APC*, *MUTYH* if *APC* is negative for variants, and screening for variants associated with Lynch syndrome.

It is important to distinguish among classical FAP, attenuated FAP, and MAP (mono- or biallelic) by genetic analysis because recommendations for patient surveillance and cancer prevention vary according to the syndrome.(3)

Testing

Genetic testing for *APC* variants may be considered in the following situations:

- Patients at high risk such as those with a family member who tested positive for FAP and have a known *APC* variant.
- Patients undergoing differential diagnosis of attenuated FAP versus *MUTYH*-associated polyposis versus Lynch syndrome. These patients do not meet the clinical diagnostic criteria for classical FAP and have few adenomatous colonic polyps.
- To confirm FAP in patients with colon cancer with a clinical picture or family history consistent with classical FAP.

Lynch syndrome

Lynch syndrome is an inherited disorder that results in a higher predisposition to CRC and other malignancies including endometrial and gastric cancer. Lynch syndrome is estimated to account for 3% to 5% of all CRC. People with Lynch syndrome have a 70% to 80% lifetime risk of developing any type of cancer.(4,5) However the risk varies by genotype. It occurs as a result of germline variant in the mismatch repair (MMR) genes that include *MLH1*, *MSH2*, *MSH6*, and *PMS2*. In approximately 80% of cases, the variants are located in the *MLH1* and *MSH2* genes, while 10% to 12% of variants are located in the *MSH6* gene and 2% to 3% in the *PMS2* gene. Also, variants in 3 additional genes (*MLH3*, *PMS1*, *EXO1*) have also been implicated with Lynch Syndrome. Notably, in individuals meeting the various clinical criteria for Lynch syndrome, 50% individuals have a variant in the *MLH1*, *MSH2*, *MSH6*, and *PMS2* genes. The lifetime risk of CRC is nearly 80% in individuals carrying a variant in one of these genes.

Testing

Preliminary screening of tumor tissue does not identify MMR gene variants but is used to guide subsequent diagnostic testing via DNA analysis for specific variants. Genetic testing or DNA analysis (gene sequencing, deletion and duplication testing) for the MMR genes involves assessment for *MLH1*, *MSH2*, *MSH6*, and *PMS2* variants. The following are 3 testing strategies.

- Microsatellite instability (MSI) testing (phenotype): Individuals with high MSI either proceed to genetic testing for *MLH1*, *MSH2*, *MSH6*, and *PMS2* or to immunohistochemical (IHC) testing.
- IHC testing (phenotype): Individuals with negative staining would proceed to genetic testing for *MLH1*, *MSH2*, *MSH6*, and *PMS2*.
- Modification strategy: Tumor tissue of patients with negative staining for *MLH1* on IHC is tested for the *BRAF* V600E variant to determine methylation status. If the *BRAF* variant is not detected, the individual receives *MLH1* DNA analysis.

The phenotype tests used to identify individuals with who may be at a high-risk of Lynch syndrome are explained next. The first screening test measures MSI. As a result of variance in the MMR gene family, the MMR protein is either absent or deficient, resulting in an inability to correct DNA replication errors causing MSI. Approximately 80% to 90% of Lynch syndrome CRC tumors have MSI. The National Cancer Institute has recommended screening for 5 markers detect MSI (Bethesda markers). MSI detection in 2 of these markers is considered a positive result or “high probability of MSI”.(6)

The second phenotype screening test is IHC, which involves staining of tumor tissue for the presence of 4 MMR proteins (*MLH1*, *MSH2*, *MSH6*, *PMS2*). The absence of one or more protein is considered abnormal.

BRAF testing is an optional screening method that may be used in conjunction with IHC testing for *MLH1* to improve efficiency. A methylation analysis of the *MLH1* gene can largely substitute for *BRAF* testing or be used in combination to improve efficiency slightly.

Both MSI and IHC have a 5% to 10% false-negative rate. MSI testing performance depends on the specific MMR variant. MSI screening has a sensitivity of about 89% for *MLH1* and *MSH2* and 77% for *MSH6* and a specificity of about 90% for each. The specificity of MSI testing is low because approximately 10% of sporadic CRCs are MSI-positive due to somatic hypermethylation of the *MLH1* promoter. Additionally, some tumors positive for *MSH6* variants are associated with the MSI-low phenotype rather than MSI-high; thus MSI-low should not be a criterion against proceeding to MMR variant testing.(7,8) IHC screening has sensitivity for *MLH1*, *MSH2*, and *MSH6* of about 83% and a specificity of about 90% for each.

Screening of tumor tissue from patients enables genetic testing for a definitive diagnosis of Lynch syndrome and leads to counseling, cancer surveillance (eg, through frequent colonoscopic or endometrial screening examinations), and prophylaxis (eg, risk-reducing colorectal or gynecologic surgeries) for CRC patients, as well as for their family members.

Genetic testing for a MMR gene variant is often limited to *MLH1* and *MSH2* and, if negative, then *MSH6* and *PMS2*. The *BRAF* gene is often mutated in CRC when a particular *BRAF* variant (V600E, a change from valine to glutamic acid at amino acid position 600 in the *BRAF*

protein) is present; to date, no *MLH1* gene variants have been reported.(9) Therefore, patients negative for *MLH1* protein expression by IHC, and therefore potentially positive for an *MLH1* variant, could first be screened for a *BRAF* variant. *BRAF*-positive samples need not be further tested by *MLH1* sequencing. *MLH1* gene methylation largely correlates with the presence of *BRAF* V600E and in combination with *BRAF* testing can accurately separate Lynch from sporadic CRC in IHC *MLH1*-negative cases.(10)

Novel deletions have been reported to affect the expression of the *MSH2* gene in the absence of a *MSH2* gene variant, and thereby cause Lynch syndrome. In these cases, deletions in *EPCAM*, the gene for the epithelial cell adhesion molecule, are responsible. *EPCAM* testing has been added to many Lynch syndrome profiles and is conducted only when tumor tissue screening results are MSI-high, and/or IHC testing shows a lack of *MSH2* expression, but no *MSH2* variant is found by sequencing. *EPCAM* is found just upstream, in a transcriptional sense, of *MSH2*. Deletions of *EPCAM* that encompass the last 2 exons of the *EPCAM* gene, including the polyadenylation signal that normally ends transcription of DNA into messenger RNA, resulting in transcriptional “read-through” and subsequent hypermethylation of the nearby and downstream *MSH2* promoter. This hypermethylation prevents normal *MSH2* protein expression and leads to Lynch syndrome in a fashion similar to Lynch cases in which an *MSH2* variant prevents *MSH2* gene expression.(11) Several studies have characterized such *EPCAM* deletions, established their correlation with the presence of *EPCAM-MSH2* fusion messenger RNAs (apparently nonfunctional) and with the presence of *MSH2* promoter hypermethylation, and, most importantly, have shown the co-segregation of these *EPCAM* variants with Lynch-like disease in families.(11-16)

Distinct from patients with *EPCAM* deletions, rare cases of Lynch syndrome have been reported without detectable germline *MMR* variants although IHC testing demonstrated a loss of expression of one of the *MMR* proteins. In at least some of these cases, research has identified germline “epivariants,” i.e., methylation of promoter regions that control the expression of the *MMR* genes.(11,17,18) Such methylation may be isolated or in conjunction with a linked genetic alteration near the affected *MMR* gene. The germline epivariants may arise de novo or may be heritable in Mendelian or non-Mendelian fashion. This is distinct from some cases of MSI-high sporadic colorectal cancer wherein the tumor tissue may show *MLH1* promoter methylation and IHC non-expression, but the same is not true of germline cells. Clinical testing for Lynch syndrome-related germline epivariants is not routine but may be helpful in exceptional cases.

Female patients with Lynch syndrome have a predisposition to endometrial cancer. Lynch syndrome is estimated to account for 2% of all endometrial cancers in women and 10% of endometrial cancers in women younger than 50 years of age. Female carriers of the germline variants *MLH1*, *MSH2*, *MSH6*, and *PMS2* have an estimated 40-62% lifetime risk of developing endometrial cancer, as well as a 4-12% lifetime risk of ovarian cancer.

Population Selection

Various attempts have been made to identify which patients with colon cancer should undergo testing for *MMR* variants, based primarily on family history and related characteristics using criteria such as the Amsterdam II criteria (19) (low sensitivity but high specificity), Revised

Bethesda guidelines (20) (better sensitivity but poorer specificity) and risk prediction models (eg, MMRpro; PREMM5; MMRpredict).(21) While family history is an important risk factor and should not be discounted in counseling families, it has poor sensitivity and specificity for identifying Lynch syndrome. Based on this and other evidence, the Evaluation of Genomic Applications in Practice and Prevention Working Group recommended testing all newly diagnosed patients with CRC for Lynch syndrome, using a screening strategy based on MSI or IHC (with or without *BRAF*) followed by sequencing in screen-positive patients. This recommendation includes genetic testing for the following types of patients:

- Family members of Lynch syndrome patients with a known MMR variant; family members would be tested only for the family variant; those testing positive would benefit from early and increased surveillance to prevent future CRC.
- Patients with a differential diagnosis of Lynch syndrome vs attenuated FAP vs MAP.
- For Lynch syndrome patients, genetic testing of the proband with CRC likely benefits the proband where Lynch syndrome is identified, and appropriate surveillance for associated malignancies can be initiated and maintained, benefiting family members by identifying the family variant.

Juvenile Polyposis Syndrome

Juvenile polyposis syndrome (JPS) is an autosomal dominant genetic disorder characterized by the presence of multiple hamartomatous (benign) polyps in the digestive tract. It is a rare disorder with an estimated incidence of 1 in 100,000 to 160,000. Generalized juvenile polyposis refers to polyps in the upper and lower gastrointestinal tract, and juvenile polyposis coli refers to polyps of the colon and rectum. Those with juvenile polyposis syndrome (JPS) are at a higher risk for colorectal and gastric cancer.(22) Approximately 60% of patients with JPS have a germline variant in either the *BMPR1A* gene or the *SMAD4* gene.(23,24) Approximately 25% of patients have de novo variants.(25,26) In most cases polyps appear in the first decade of life and most patients are symptomatic by age 20 years.(27) Rectal bleeding is the most common presenting symptom, occurring in more than half of patients. Other presenting symptoms include prolapsing polyp, melena, pain, iron deficiency anemia, and diarrhea.(22,26,27)

As noted, individuals with JPS are at increased risk for colorectal and gastric cancer. By 35 years of age, the cumulative risk of colorectal cancer is 17% to 22% which rises to 68% by age 60 years.(28,29) The estimated lifetime risk of gastric cancer is 20% to 30% with a mean age at diagnosis of 58 years.(22,26,28) JPS may also be associated with hereditary hemorrhagic telangiectasia.(30) The most common clinical manifestations of hereditary hemorrhagic telangiectasia are telangiectasias of the skin and buccal mucosa, epistaxis, and iron deficiency anemia from bleeding.

Diagnosis

A clinical diagnosis of JPS is made on the basis of presence of any one of the following: at least five juvenile polyps in the colon or multiple juvenile polyps in other parts of the gastrointestinal tract or any number of juvenile polyps in a person with a known family history of juvenile polyps.(31) It is recommended that individuals who meet clinical criteria for JPS

should undergo genetic testing for a germline mutation in the *BMPR1A* and *SMAD4* genes for a confirmatory diagnosis of JPS and to counsel at-risk family members. If there is a known *SMAD4* variant in the family, genetic testing should be performed within the first six months of life due to hereditary hemorrhagic telangiectasia risk.(98)

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome (PJS) is also an autosomal dominant genetic disorder, similar to JPS and is characterized by the presence of multiple hamartomatous (benign) polyps in the digestive tract, mucocutaneous pigmentation, and an increased risk of gastrointestinal and non-gastrointestinal cancer. It is a rare disorder with an estimated incidence of 1 in 8000 to 200,000. In most cases, germline variant in the *STK11* (*LKB1*) gene is responsible for PJS, which has a high penetrance of over 90% by the age of 30 years.(32-34) However, 10% to 20% of individuals with PJS have no family history and are presumed to have PJS due to de novo mutations.(35) Variant in *STK11* are detected in only 50% to 80% of families with PJS, suggesting that there is a second PJS gene locus.

The reported lifetime risk for any cancer is between 37% and 93% among those diagnosed with PJS with an average age of cancer diagnosis at 42 years. The most common sites for malignancy are colorectal, followed by breast, stomach, small bowel, and pancreas.(36) The estimated lifetime risk of gastrointestinal cancer ranges from 38% to 66%.(36) Lifetime cancer risk stratified by organ site is colorectal (39%), stomach (29%), small bowel (13%), and pancreas (11 to 36%).

Diagnosis

A clinical diagnosis of PJS is made on the basis if an individual meets two or more of the following criteria: presence two or more histologically confirmed PJ polyps of the small intestine or characteristic mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, or fingers or family history of PJS.(31) Individuals who meet clinical criteria for PJS should undergo genetic testing for a germline mutation in the *STK11* gene for a confirmatory diagnosis of PJS and to counsel at-risk family members.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Genetic tests reviewed in this evidence review are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Medical Policy Statement

Genetic testing for polyposis and non-polyposis cancer syndromes is established. They are considered useful diagnostic options for individuals who meet clinical criteria for increased risk of hereditary colorectal cancer.

Inclusionary and Exclusionary Guidelines

Inclusions:

These guidelines refer to the different types of genetic tests available for colorectal cancer (CRC).

A. Genetic testing of the adenomatous polyposis coli gene (APC) is established in any of the following:

- At risk^a (first- and second-degree) relatives of individuals with familial adenomatous polyposis (FAP) or attenuated familial adenomatous polyposis (AFAP) and/or a known APC variant; **OR**
- Individuals with a differential diagnosis of attenuated FAP versus *MUTYH*-associated polyposis (MAP) versus Lynch syndrome. Whether testing begins with APC variants or screening for mismatch repair *MMR* variants depends on clinical presentation.

^aDue to the high lifetime risk of cancer of the majority of the genetic syndromes discussed in this policy, “at-risk relatives” primarily refers to first-degree (i.e. siblings, parents, and offspring) and second-degree (i.e. grandparents, aunts, uncles, nieces, nephews, grandchildren and half-siblings) relatives. However, some judgment must be allowed, for example, in the case of a small family pedigree, when extended family members may need to be included in the testing strategy.

*It is recommended that, when possible, initial genetic testing for familial adenomatous polyposis (FAP) or Lynch syndrome be performed in an affected family member so that testing in unaffected family members can focus on the variant found in the affected family member. If an affected family member is not available for testing, testing should begin with an unaffected family member most closely related to an affected family member.

B. Genetic testing of the *MUTYH* gene is established in all of the following:

- Individuals with a differential diagnosis of attenuated familial adenomatous polyposis (FAP) vs *MUTYH*-associated polyposis (MAP) vs Lynch syndrome; **AND**
- Negative result for APC gene variants; **AND**
- Negative family history of no parents or children with FAP is consistent with autosomal recessive MAP.

*In many cases, genetic testing for *MUTYH* gene variants should first target the specific variants Y165C and G382D, which account for more than 80% of variants in white populations, and subsequently proceed to sequencing only as necessary. In other ethnic populations, however, proceeding directly to sequencing is appropriate.

C. Genetic testing of *MMR* genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) to determine the carrier status of Lynch syndrome is established in any of the following:

- Individuals with colorectal cancer with tumor testing suggesting germline *MMR* deficiency or meeting clinical criteria for Lynch syndrome; **OR**
- Individuals with endometrial cancer with tumor testing suggesting germline *MMR* deficiency or meeting clinical criteria for Lynch syndrome; **OR**
- At-risk^a (first- and second-degree) relatives of patients with Lynch syndrome with a known *MMR* variant; **OR**

- Individuals with a differential diagnosis of attenuated FAP versus MAP versus Lynch syndrome. Whether testing begins with *APC* variants or screening for *MMR* genes depends on clinical presentation; **OR**
- Individuals without colorectal cancer but with a family history meeting the Amsterdam or Revised Bethesda criteria, or documentation of 5% or higher predicted risk of the syndrome on a validated risk prediction model (e.g. MMRpro, PREMM5 or MMRpredict) when:
 - No affected family members have been tested for *MMR* variants.

**For patients with colorectal cancer (CRC) or endometrial cancer being evaluated for Lynch syndrome, the microsatellite instability (MSI) test, or the immunohistochemical (IHC) test with or without BRAF gene variant testing, or methylation testing, should be used as an initial evaluation of tumor tissue before mismatch repair MMR gene analysis. Both tests are not necessary. Proceeding to MMR gene sequencing would depend on results of MSI or IHC testing. In particular, IHC testing may help direct which MMR gene likely contains a variant, if any, and may also provide additional information if MMR genetic testing is inconclusive.*

**When indicated, genetic sequencing for MMR gene variants should begin with MLH1 and MSH2 genes, unless otherwise directed by the results of IHC testing. Standard sequencing methods will not detect large deletions or duplications; when MMR gene variants are expected based on IHC or MSI studies but none are found by standard sequencing, additional testing for large deletions or duplications is appropriate.*

D. Genetic testing of the *EPCAM* gene is established when any of the following major criteria (solid bullets) is met:

- Individuals with colorectal cancer, for the diagnosis of Lynch syndrome in one of the following:
 - Tumor tissue shows lack of *MSH2* protein expression by immunohistochemistry and patient is negative for a *MSH2* germline variant; **OR**
 - Tumor tissue shows a high level of microsatellite instability and patient is negative for a germline variant in *MSH2*, *MLH1*, *PMS2*, and *MSH6*; **OR**
- At-risk^a (first- and second-degree) relatives of patients with Lynch syndrome with a known pathogenic/likely pathogenic *EPCAM* variant; **OR**
- Individuals without colorectal cancer but with a family history meeting the Amsterdam or Revised Bethesda criteria, or documentation of 5% or higher predicted risk of the syndrome on a validated risk prediction model (e.g. MMRpro, PREMM5 or MMRpredict) when both of the following are met:
 - No affected family members have been tested for *MMR* variants; **AND**
 - Sequencing for *MMR* variants is negative.

The Amsterdam II Clinical Criteria (all criteria must be fulfilled) are the most stringent criteria for defining families at high risk for Lynch syndrome (Vasen et al, 1999):

- *Three or more relatives with an associated cancer (colorectal cancer, or cancer of the endometrium, small intestine, ureter, or renal pelvis);*
- *One should be a first-degree relative of the other two;*
- *Two or more successive generations affected;*
- *One or more relatives diagnosed before the age of 50 years;*
- *Familial adenomatous polyposis (FAP) should be excluded in cases of colorectal carcinoma;*
- *Tumors should be verified by pathologic examination.*
- *Modifications:*

- *EITHER: very small families, which cannot be further expanded, can be considered to have hereditary nonpolyposis colorectal cancer (HNPCC) with only two colorectal cancers in first degree relatives if at least two generations have the cancer and at least one case of colorectal cancer was diagnosed by the age of 55 years; or*
- *In families with two first-degree relatives affected by colorectal cancer, the presence of a third relative with an unusual early-onset neoplasm or endometrial cancer is sufficient.*

The Revised Bethesda Guidelines (fulfillment of any criterion meets guidelines) are less strict than the Amsterdam criteria and are intended to increase the sensitivity of identifying at-risk families (Umar et al, 2004). The Bethesda guidelines are also considered more useful in identifying which patients with colorectal cancer should have their tumors tested for microsatellite instability and/or immunohistochemistry:

- *Colorectal carcinoma (CRC) diagnosed in a patient who is less than 50 years old;*
- *Presence of synchronous or metachronous CRC or other HNPCC-associated tumors, *regardless of age;*
- *CRC with high microsatellite instability histology diagnosed in a patient less than 60 years old;*
- *CRC diagnosed in one or more first-degree relatives with a Lynch syndrome-associated tumor, with one of the cancers being diagnosed at younger than 50 years of age;*
- *CRC diagnosed in two or more first or second-degree relatives with HNPCC-related tumors, *regardless of age.*

** HNPCC-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain [usually glioblastoma as seen in Turcot syndrome], sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel.*

E. Somatic genetic testing for *BRAF V600E* or *MLH1* promoter methylation are established to exclude a diagnosis of Lynch syndrome when:

- **MLH1 protein is not expressed in a colorectal cancer tumor on immunohistochemical analysis.**

F. Genetic testing of *SMAD4* and *BMPR1A* genes are established when any of the following major criteria (solid bullets) is met:

- **Individual has a clinical diagnosis of juvenile polyposis syndrome based on the presence of any one of the following:**
 - **At least five juvenile polyps in the colon **OR****
 - **Multiple juvenile polyps throughout the gastrointestinal tract **OR****
 - **Any number of juvenile polyps in a person with a known family history of juvenile polyps **OR****
- **Individual is an at-risk relative of a patient suspected of or diagnosed with juvenile polyposis syndrome.**

G. Genetic testing for *STK11* gene variants is established when any of the following major criteria (solid bullets) is met:

- **Individual has a clinical diagnosis of Peutz-Jeghers syndrome based on the presence of any two of the following secondary criteria:**
 - **Presence of two or more histologically confirmed Peutz-Jeghers polyps of the small intestine **OR****
 - **Characteristic mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, or fingers **OR****
 - **Family history of Peutz-Jeghers syndrome **OR****
- **Individual is an at-risk^a relative of a patient suspected of or diagnosed with Peutz-Jeghers syndrome.**

Pre- and post-test genetic counseling is established as an adjunct to genetic testing.

** Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.*

Exclusions:

Testing for germline *APC* gene variants for inherited CRC syndromes is considered experimental/investigational in all other situations.

Testing for germline *MUTYH* gene variants for inherited CRC syndromes is considered experimental/investigational in all other situations.

Testing for germline MMR gene variants for inherited CRC syndromes is considered experimental/investigational in all other situations.

Testing for somatic *BRAF V600E* or *MLH1* promoter methylation to exclude a diagnosis of Lynch syndrome is considered experimental/investigational in all other situations.

Testing for germline *SMAD4* and *BMPR1A* gene variants for inherited CRC syndromes is considered experimental/investigational in all other situations.

Testing for germline *STK11* gene variants for inherited CRC syndromes is considered experimental/investigational in all other situations.

Genetic testing for all other genes for an inherited CRC syndrome is considered experimental/investigational.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

Genetic Testing in Patients at Risk for FAP:

81201 81202 81203

Genetic Testing in Patients at Risk for Lynch Syndrome formerly hereditary non-polyposis colorectal cancer (HNPCC):

| | | | | | | |
|-------|--------|-------|--------|-------|-------|-------|
| 81210 | 81288 | 81292 | 81293 | 81294 | 81295 | 81296 |
| 81297 | 81298 | 81299 | 81300 | 81301 | 81317 | 81318 |
| 81319 | 81401* | 81403 | 81406* | 81435 | | |

* 81401 and 81406 include *MUTYH* (eg, MYH-associated polyposis)

Other codes (investigational, not medically necessary, etc.):

81327 0238U

Rationale

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

GENETIC TESTING FOR FAMILIAL ADENOMATOUS POLYPOSIS AND *MUTYH*-ASSOCIATED POLYPOSIS

Clinical Context and Text Purpose

The purpose of genetic testing for familial adenomatous polyposis (FAP) and *MUTYH*-associated polyposis is to:

- Identify at-risk relatives of individuals with FAP and/or a known adenomatous polyposis coli (*APC*) gene variant
- Make a differential diagnosis of attenuated FAP vs *MUTYH*-associated polyposis (MAP) vs Lynch syndrome.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is at-risk relatives of individuals with FAP and/or a known *APC* variant or those who require a differential diagnosis of attenuated FAP vs MAP vs Lynch syndrome.

Interventions

The relevant intervention is genetic testing for *APC* or *MUTYH*. Commercial testing is available from numerous companies.

Comparators

The following practice is currently being used to make decisions about managing FAP and MUTYH-associated polyposis: no genetic testing.

Outcomes

The potential beneficial outcomes of primary interest would be early detection of colorectal cancer (CRC) and appropriate and timely interventional strategies (eg, endoscopic resection, colectomy) to prolong life.

The potential harmful outcomes are those resulting from a false test result. False-positive or -negative test results can lead to the initiation of unnecessary treatment and adverse events from that treatment or undertreatment.

Genetic testing for FAP may be performed at any point during a lifetime. The necessity for genetic testing is guided by the availability of information that alters the risk of an individual of having or developing FAP.

Study Selection Criteria

For the evaluation of clinical validity of the genetic test, studies that meet the following eligibility criteria were considered:

- Reported on the analytic sensitivity and specificity and/or diagnostic yield of the test.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

The evidence review for FAP genetic testing was originally informed by a TEC Assessment. (1998) (37) Additional information on attenuated FAP and on MAP diagnostic criteria and genetic testing is based on several publications that build on prior cited research. (39-42)

Clinical sensitivity for classic FAP is about 95%; about 90% of pathogenic variants are detected by sequencing (38,43) while 8% to 12% of pathogenic variants are detected by deletion and duplication testing.(44,45) Among Northern European whites, 98% of pathogenic *MUTYH* variants are detected by full gene sequencing.(46,47)

A comprehensive review of the *APC* pathogenic variant and its association with classical FAP and attenuated FAP and MAP is beyond the scope of this evidence review. *GeneReviews* (38) reported that the likelihood of detecting an *APC* pathogenic variant is highly dependent on the severity of colonic polyposis (44,48-50) and family history.(51) Detection rates are higher in classic polyposis (88%) than in nonclassical FAPs such as attenuated colonic phenotypes (57%) or MAP (33%).

Clinical Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

No RCTs were identified assessing the clinical utility of genetic testing for FAP and MUTYH-associated polyposis.

Chain of Evidence

Genetic testing of patients requiring a differential diagnosis of attenuated FAP vs MAP vs Lynch syndrome may have clinical utility:

- If the test supports the clinical diagnosis of an attenuated disease, the protocol for endoscopic surveillance is affected and, depending on the situation, may avoid more frequent but unnecessary surveillance or necessitates more frequent surveillance.

Genetic testing of at-risk relatives of patients with FAP and/or a known *APC* variant may have clinical utility:

- If, in the absence of genetic testing, the diagnosis of colorectal polyposis in at-risk relatives of patients with FAP and/or a known *APC* variant can only be established by colonoscopy and subsequent histologic examination of removed polyps, which are burdensome.
- If results are negative, the test results may provide release from intensified screening program resulting in psychological relief.

The TEC Assessment (1998) (37) offered the following conclusions:

- Genetic testing for FAP may improve health outcomes by identifying which currently unaffected at-risk family members require intense surveillance or prophylactic colectomy.
- At-risk subjects are considered to be those with greater than 10 adenomatous polyps; or close relatives of patients with clinically diagnosed FAP or of patients with an identified adenomatous polyposis (*APC*) variant.
- The optimal testing strategy is to define the specific genetic variant in an affected family member and then test the unaffected family members to see if they have inherited the same variant.

Testing for the *APC* variant has no role in the evaluation, diagnosis, or treatment of patients with classical FAP where the diagnosis and treatment are based on the clinical presentation.

Section Summary: Genetic Testing for Familial Adenomatous Polyposis and MUTYH-Associated Polyposis

The analytic and clinical sensitivity and specificity for *APC* and *MUTYH* were high. About 90% of pathogenic variants in classical FAP are detected by sequencing while 8% to 12% of pathogenic variants are detected by deletion and duplication testing. Among Northern European whites, 85% of pathogenic *MUTYH* variants are detected by the 2-variant test, and 98% of pathogenic *MUTYH* variants are detected by full gene sequencing. The likelihood of detecting an *APC* pathogenic variant is highly dependent on the severity of colonic polyposis and family history. Detection rates are higher in classic polyposis (88%) than in nonclassical FAPs such as attenuated colonic phenotypes (57%) or MAP (33%). Direct evidence of clinical utility for genetic testing of FAP is not available. Genetic testing of at-risk relatives of patients with FAP and/or a known *APC* variant or those requiring a differential diagnosis of attenuated

FAP vs MAP vs Lynch syndrome may have clinical utility by avoiding burdensome and invasive endoscopic examinations, release from intensified screening program resulting in psychological relief, and may improve health outcomes by identifying which currently unaffected at-risk family members require intense surveillance or prophylactic colectomy.

LYNCH SYNDROME AND COLORECTAL CANCER GENETIC TESTING

Clinical Context and Test Purpose

The purpose of genetic testing for Lynch syndrome is to:

- Detect Lynch syndrome in individuals diagnosed with colorectal or endometrial cancer
- Identify at-risk relatives of individuals with a diagnosed Lynch syndrome and/or a known mismatch repair (MMR) variant and/or positive family history meeting the Amsterdam or Revised Bethesda criteria, or documentation of 5% or higher predicted risk of the syndrome on a risk prediction model,
- Make a differential diagnosis of attenuated FAP v MAP vs Lynch syndrome.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals diagnosed with colorectal or endometrial cancer or at-risk relatives of patients with a diagnosed Lynch syndrome and/or a known MMR variant and/or positive family history meeting the Amsterdam or Revised Bethesda criteria or documentation of 5% or higher predicted risk of the syndrome on a risk prediction model, or those requiring a differential diagnosis of attenuated FAP vs MAP vs Lynch syndrome.

Interventions

The relevant intervention is genetic testing for *MLH1*, *MSH2*, *MSH6*, *PMS2*, and/or *EPCAM* genes. Commercial testing is available from numerous companies.

Comparators

The following practice is currently being used to make decisions about managing Lynch syndrome: no genetic testing.

Outcomes

The potential beneficial outcomes of primary interest would be early detection of Lynch syndrome and appropriate and timely interventional strategies (eg, increased surveillance, endoscopic resection, colectomy) to prolong life.

The potential harmful outcomes are those resulting from a false-test result. False-positive or -negative test results can lead to the initiation of unnecessary treatment and adverse effects from that treatment or undertreatment.

Genetic testing for Lynch syndrome may be performed at any point during a lifetime. The necessity for genetic testing is guided by the availability of information that alters the risk of an individual having or developing Lynch syndrome.

Study Selection Criteria

For the evaluation of clinical validity of the genetic test, studies that meet the following eligibility criteria were considered:

- Reported on the analytic sensitivity and specificity and/or diagnostic yield of the test.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

MMR Genes

Microsatellite instability (MSI) and immunohistochemical (IHC) screening tests for MMR variants have similar sensitivity and specificity. MSI screening has a sensitivity of about 89% for *MLH1* and *MSH2* and 77% for *MSH6* and a specificity of about 90% for all. IHC screening has sensitivity for *MLH1*, *MSH2*, and *MSH6* of about 83% and a specificity of about 90% for each.

The evidence for Lynch syndrome genetic testing in patients with colorectal cancer (CRC) is based on an evidence report conducted for the Agency for Healthcare Research and Quality by Bonis et al (2007),(52) a supplemental assessment to that report contracted by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group,(9) and an EGAPP recommendation (2009) for genetic testing in CRC.(53) Based on the AHRQ report and supplemental assessment, the EGAPP recommendation concluded the following about genetic testing for *MMR* variants in patients already diagnosed with CRC:

- Family history, while important information to elicit and consider in each case, has poor sensitivity and specificity as a screening test to determine who should be considered for *MMR* variant testing and should not be used as a sole determinant or screening test.
- Optional *BRAF* testing can be used to reduce the number of patients, who are negative for *MLH1* expression by IHC, needing *MLH1* gene sequencing, thus improving efficiency without reducing sensitivity for *MMR* variants.

Vos et al (2020) evaluated the yield to detect Lynch syndrome in a prospective cohort of 3602 newly diagnosed CRC cases below age 70. (82) The standard testing protocol included IHC or MSI testing, followed by *MLH1* hypermethylation testing. Testing identified *MLH1* hypermethylation in a majority of cases tested (66% of 264). The percentage of MMR deficient CRC explained by hypermethylation increased with age, while the percentage of patients with hereditary CCR decreased with age. Of the 47 patients who underwent genetic testing, 55% (26/47) were determined to have Lynch syndrome. The authors estimated that only 78% of these cases would have been identified by the revised Bethesda guidelines. The percentage by age was 86% (6/7) in those under 40 years, 57% (17/29) in patients aged 40 to 64 years, and 30% (3/10) in patients 65 to 69 years of age and the number needed to test to identify 1 case of Lynch syndrome after prescreening was 1.2 (95% CI: 1.0 to 2.0) in patients under 40 years, 4.1 (95% CI: 3.1 to 5.5) in patients 40 to 64 years of age, and 21 (95% confidence interval [CI]: 11 to 43) in CRC patients aged 65 to 69.

Tsuruta et al (2022) performed IHC screening for MMR-related genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) to determine the extent to which Lynch syndrome can be diagnosed in patients with endometrial cancer through universal screening.(83) Samples were obtained from 100 patients, and 19 patients with lost results for any of the proteins were identified. The MSI-high

phenotype was identified in 16 of 19 patients and MLH1 methylation was identified in 11 of 19 patients. The following were also detected: 2 pathological variants (MSH2 and MSH6), 2 cases of unclassified variant (MSH6), and 1 case of benign variant (PMS2).

EPCAM Testing

Several studies have characterized *EPCAM* deletions, established their correlation with the presence of *EPCAM-MSH2* fusion messenger RNAs (apparently nonfunctional) and with the presence of *MSH2* promoter hypermethylation, and, most importantly, have shown the co-segregation of these *EPCAM* variants with Lynch-like disease in families.(11-16) Because studies differ slightly in how patients were selected, the prevalence of these *EPCAM* variants is difficult to estimate but may be in the range of 20% to 40% of patients/families who meet Lynch syndrome criteria, do not have an MMR variant, but have MSI-high tumor tissue. Kempers et al (2011) reported that carriers of an *EPCAM* deletion had a 75% (95% CI, 65% to 85%) cumulative risk of CRC by age 70 years, which did not differ significantly from that of carriers of an *MSH2* deletion (77%; 95% CI, 64% to 90%). The mean age at diagnosis was 43 years.(54) However, the cumulative risk of endometrial cancer was low at 12% (95% CI, 0% to 27%) by age 70 compared with carriers of an *MSH2* variant (51%; 95% CI, 33% to 69%; $p < 0.001$).

BRAF V600 or MLH1 Promoter Methylation

Jin et al (2013) evaluated MMR proteins in 412 newly diagnosed CRC patients.(55) MLH1 and PMS2 protein stains were absent in 65 (72%) patients who were subsequently tested for *BRAF* variant. Thirty-six (55%) of the 65 patients had the *BRAF V600E* variant, thus eliminating the need for further genetic testing or counseling for Lynch syndrome. Capper et al (2013) reported on a technique of VE1 IHC testing for *BRAF* variants on a series of 91 MSI-H CRC patients.(56) The authors detected *BRAF*-mutated CRC with 100% sensitivity and 98.8% specificity. V600E positive lesions were detected in 21% of *MLH1*-negative CRC patients who could be excluded from *MMR* germline testing for Lynch syndrome. Therefore, V600E IHC testing for *BRAF* could be an alternative to *MLH1* promoter methylation analysis. To summarize, *BRAF* variant *V600E* variant or *MLH1* promoter methylation testing are optional screening methods that may be used when IHC testing shows a loss of *MLH* protein expression. The presence of *BRAF V600E* or absence of *MLH1* protein expression due to *MLH1* promoter methylation rarely occurs in Lynch syndrome and would eliminate the need for further germline variant analysis for a Lynch syndrome diagnosis.(57)

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No RCTs were identified assessing the clinical utility of genetic testing for Lynch syndrome.

Chain of Evidence

Genetic testing of patients with colon or endometrial cancer to detect Lynch syndrome has clinical utility:

- To make decisions about preferred approach for treatment (endoscopic resection, colectomy with ileorectal anastomosis or segmental colectomy).

Genetic testing of at-risk relatives of patients with Lynch syndrome and/or a known MMR variant and/or positive family history meeting the Amsterdam or Revised Bethesda criteria, or documentation of 5% or higher predicted risk of the syndrome on a risk prediction model, has clinical utility:

- If the individuals diagnosed with Lynch syndrome are recommended for screening for Lynch syndrome-associated cancers.
- If, in the absence of genetic testing, the diagnosis of Lynch syndrome in at-risk relatives of patients can only be established by colonoscopy and subsequent histologic examination of excised polyps, which is burdensome.
- If negative test results prompt release from an intensified screening program, thereby reducing in emotional burden.

Genetic testing of patients requiring a differential diagnosis of attenuated FAP vs MAP vs Lynch syndrome may have clinical utility:

- If the test supports the clinical diagnosis of Lynch syndrome, the protocol for endoscopic surveillance is affected and, depending on the situation, may avoid more frequent but unnecessary surveillance or necessitates more frequent surveillance.

A chain of evidence can be constructed for the clinical utility of testing all patients with CRC for MMR variants. EGAPP conclusions are summarized next.

1. The chain of evidence from well-designed experimental nonrandomized studies is adequate to demonstrate the clinical utility of testing unaffected (without cancer) first- and second-degree relatives of patients with Lynch syndrome who have a known MMR variant.
2. Seven studies examined how counseling affected testing and surveillance choices among unaffected family members of Lynch syndrome patients.(60-66) About half of relatives received counseling, and 95% of these chose MMR gene variant testing. Among those positive for MMR gene variants, uptake of colonoscopic surveillance beginning at age 20 to 25 years was high at 53% to 100%.
 - One long-term, nonrandomized controlled study and a cohort study of Lynch syndrome family members found significant reductions in CRC among those who followed recommended colonic surveillance vs those who did not.
 - Surveillance, prevention for other Lynch syndrome cancers.
3. The chain of evidence from descriptive studies and expert opinion is inadequate (inconclusive) to demonstrate the clinical utility of testing the probands with Lynch syndrome (i.e., cancer index patient).
 - Subtotal colectomy is recommended as an alternative to segmental resection but has not been shown superior in follow-up studies

- Although a small body of evidence suggests that MSI-positive tumors are resistant to 5-fluorouracil and more sensitive to irinotecan than MSI-negative tumors, no alteration in therapy according to MSI status has yet been recommended.
- Surveillance, prevention for other Lynch syndrome cancers:
 - While invasive and not actively recommended, women may choose hysterectomy with salpingo-oophorectomy to prevent gynecologic cancer. In a retrospective study (2006), of 315 women who chose this option had no gynecologic cancer over 10 years, whereas about one-third of women who did not have surgery developed endometrial cancer, and 5.5% developed ovarian cancer.(67)
 - In a study by Bouzourene et al (2010), surveillance endometrial biopsy detected endometrial cancer and potentially precancerous conditions at earlier stages in those with Lynch syndrome, but results were not statistically significant, and a survival benefit has yet to be shown.(10) Transvaginal ultrasound (TVUS) is not a highly effective surveillance mechanism for endometrial cancer in patients with Lynch syndrome; however, TVUS in conjunction with endometrial biopsy has been recommended for surveillance.
 - Gastroduodenoscopy for gastric cancer surveillance and urine cytology for urinary tract cancer surveillance are recommended based on expert opinion only, in the absence of adequate supportive evidence.

The Cancer Genetic Studies Consortium (1997) recommended that if CRC is diagnosed in patients with an identified variant or a strong family history, a subtotal colectomy with ileorectal anastomosis should be considered as an option to segmental resection.(68) The 2006 joint American Society of Clinical Oncology and Society of Surgical Oncology review assessing risk-reducing surgery in hereditary cancers recommended offering both options to patients with Lynch syndrome and CRC, especially those who are younger.(69) The Societies' review also recommended offering Lynch syndrome patients with an index rectal cancer the options of total proctocolectomy with ileal pouch anal anastomosis or anterior proctosigmoidectomy with primary reconstruction. The rationale for total proctocolectomy is the 17% to 45% rate of metachronous colon cancer in the remaining colon after an index rectal cancer in Lynch syndrome patients.

The risk of endometrial cancer in MMR variant carriers has been estimated at 34% (95% CI, 17% to 60%) by age 70, and at 8% for ovarian cancer (95% CI, 2% to 39%) by age 70. (58) Risks do not appear to appreciably increase until after age 40. Females with Lynch syndrome who choose risk-reducing surgery are encouraged to consider oophorectomy because of the risk of ovarian cancer in Lynch syndrome. In a retrospective cohort study, Obermair et al (2010) found that hysterectomy improved survival among female colon cancer survivors with Lynch syndrome. (71) This study estimated that, for every 100 women diagnosed with Lynch syndrome-associated CRC, about 23 would be diagnosed with endometrial cancer within 10

years absent a hysterectomy. Surveillance in Lynch syndrome populations for ovarian cancer has not been demonstrated to be successful at improving survival. (72)

Section Summary: Lynch Syndrome and Colorectal Cancer Genetic Testing

Direct evidence of clinical utility for genetic testing for Lynch syndrome is not available. Multiple studies have demonstrated clinical utility in testing unaffected (without cancer) first- and second-degree relatives of patients with Lynch syndrome who have a known MMR variant, in that counseling has been shown to influence testing and surveillance choices among unaffected family members of Lynch syndrome patients. One long-term, nonrandomized controlled study and 1 cohort study of Lynch syndrome family members found significant reductions in CRC among those who followed and did not follow recommended colonic surveillance. A positive genetic test for an MMR gene variant can also lead to changes in the management of other Lynch syndrome malignancies.

GENETIC TESTING FOR JUVENILE POLYPOSIS SYNDROME AND PEUTZ-JEGHERS SYNDROME:

Clinical Context and Test Purpose

The purpose of genetic testing for juvenile polyposis syndrome (JPS) and Peutz-Jeghers syndrome (PJS) is to:

- To confirm a diagnosis of JPS or PJS in individuals suspected of these disorders based on clinical features
- To identify at-risk relatives of individuals with a confirmed diagnosis of JPS or PJS.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest are individuals suspected of JPS or PJS or individuals who are at-risk relatives of individuals suspected of or diagnosed with a polyposis syndrome or PJS.

Interventions

The relevant intervention is genetic testing for SMAD4 and BMPR1 (for JPS) and ASATK11 (for PJS). Commercial testing is available from numerous companies.

Comparators

The following practice is currently being used to make decisions about managing JPS and PJS: no genetic testing.

Outcomes

The potential beneficial outcomes of primary interest would be early detection of cancer and appropriate and timely interventional strategies (eg, cancer screening, surgical intervention including polyp resection, gastrectomy, colectomy) to prolong life.

The potential harmful outcomes are those resulting from a false test result. False-positive or -negative test results can lead to the initiation of unnecessary treatment and adverse events from that treatment or undertreatment.

Genetic testing for SMAD4 and BMPR1 (for JPS) and ASATK11 (for PJS) may be performed at any point during a lifetime. The necessity for genetic testing is guided by the availability of information that alters the risk of an individual of having or developing JPS and PJS.

Study Selection Criteria

For the evaluation of clinical validity of the genetic test, studies that meet the following eligibility criteria were considered:

- Reported on the diagnostic yield of the test.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Table 1 summarizes the clinical validity studies assessing genetic testing for JPS and PJS.

| Study | Study Design and Population | Results |
|--------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| Calva-Cerqueira et al (2009) ⁷³ | Observational; 102 unrelated JPS probands analyzed all of whom met clinical criteria for JPS | SMAD4 and BMPR1A variants detected in 41% (42/102) JPS probands |
| Aretz et al (2007) ⁷⁴ | Observational; 80 unrelated patients (65 met clinical criteria for typical JPS; 15 presumed to have JPS) were examined by direct sequencing for SMAD4, BMPR1A, and PTEN variants | SMAD4 and BMPR1A variants detected in 60% of typical JPS patients and none in presumed JPS patients; overall diagnostic yield, 49% |
| Volikos et al (2006) ⁷⁵ | Observational; 76 clinically diagnosed with PJS | Detection rate of germline variants was about 80% (59/76) |
| Aretz et al (2005) ⁷⁶ | Observational; 71 patients (56 met clinical criteria for PJS; 12 presumed to have PJS) | STK11 variant detected in 52% (37/71) |

JPS: juvenile polyposis syndrome; PJS: Peutz-Jeghers syndrome.

Clinical Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No RCTs were identified assessing the clinical utility of genetic testing for JPS and PJS.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Genetic testing of patients suspected with JPS and PJS has clinical utility:

- To make decisions about preferred approach for treatment (endoscopic resection, colectomy with ileorectal anastomosis or segmental colectomy).

Genetic testing of individuals who are at-risk relatives of patients suspected of or diagnosed with a JPS or PJS has clinical utility:

- If the individuals diagnosed with JPS and PJS are recommended for screening for JPS and PJS-associated cancers.
- If, in the absence of genetic testing, the diagnosis of JPS and PJS in at-risk relatives of patients can only be established by colonoscopy and subsequent histologic examination of excised polyps, which is burdensome.
- If negative test results prompt release from an intensified screening program, thereby reducing in emotional burden.

A systematic review of 20 cohort studies with a total of 1644 patients with PJS was published by Lier et al (2010). (36) A total of 349 patients developed 384 malignancies at average age of 42 y. Lifetime risk for any cancer varied between 37% and 93% with RRs ranging from 9.9 to 18 vs the general population.

Section Summary: Genetic Testing for Juvenile Polyposis Syndrome and Peutz-Jeghers Syndrome

The likelihood of detecting a pathogenic variant is highly dependent on the presence of clinical features and family history. Detection rates for JPS and PJS have been reported to be between 60 to 41% and 29.4% to 80%, respectively. Direct evidence of clinical utility for genetic testing of a JPS or PJS is not available. Genetic testing of patients suspected of JPS or PJS or individuals who are at-risk relatives of patients suspected of or diagnosed with a polyposis syndrome or PJS may have clinical utility by avoiding burdensome and invasive endoscopic examinations, release from intensified screening program resulting in psychological relief, and improving health outcomes by identifying which currently unaffected at-risk family members require intense surveillance or prophylactic colectomy.

SUMMARY OF EVIDENCE

For individuals who are suspected of attenuated familial adenomatous polyposis (FAP), MUTYH-associated polyposis (MAP), and Lynch syndrome, or are at-risk relatives of patients with FAP who receive genetic testing for adenomatous polyposis coli (APC), the evidence includes a TEC Assessment. Relevant outcomes are overall survival (OS), disease-specific survival, and test accuracy and validity. For patients with an APC variant, enhanced surveillance and/or prophylactic treatment will reduce the future incidence of colon cancer and improve health outcomes. A related familial polyposis syndrome, MAP syndrome, is associated with variants in the MUTYH gene. Testing for this genetic variant is necessary when the differential diagnosis includes both FAP and MAP because distinguishing between the two leads to different management strategies. Depending on presentation, Lynch syndrome may

be part of the same differential diagnosis. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who (1) are suspected of attenuated FAP, MAP, and Lynch syndrome, (2) have colon cancer, (3) have endometrial cancer meeting clinical criteria for Lynch syndrome, (4) are at-risk relatives of patients with Lynch syndrome, (5) are without colon cancer but with a family history meeting the Amsterdam or Revised Bethesda criteria, or documentation of 5% or higher predicted risk of the syndrome on a validated risk prediction model, who receive genetic testing for mismatch repair (MMR) genes, the evidence includes an Agency for Healthcare Research and Quality report, a supplemental assessment to that report by the Evaluation of Genomic Applications in Practice and Prevention Working Group, and an Evaluation of Genomic Applications in Practice and Prevention recommendation for genetic testing in colorectal cancer (CRC). Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. A chain of evidence from well-designed experimental nonrandomized studies is adequate to demonstrate the clinical utility of testing unaffected (without cancer) first- and second-degree relatives of patients with Lynch syndrome who have a known variant in an MMR gene, in that counseling has been shown to influence testing and surveillance choices among unaffected family members of Lynch syndrome patients. One long-term, nonrandomized controlled study and a cohort study of Lynch syndrome family members found significant reductions in CRC among those who did and did not follow recommended colonic surveillance. A positive genetic test for an MMR variant can also lead to changes in the management of other Lynch syndrome malignancies. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who warrant Lynch testing, screen negative on MMR testing, but positive for microsatellite instability (MSI) and lack MSH2 protein expression who receive genetic testing for EPCAM variants, the evidence includes variant prevalence studies and case series. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. Studies have shown an association between EPCAM variants and Lynch-like disease in families, and the cumulative risk for CRC is similar to carriers of an MSH2 variant. Identification of an EPCAM variant could lead to changes in management that improve health outcomes. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have CRC in whom MLH1 protein is not expressed on immunohistochemical analysis (IHC) and who receive genetic testing for BRAF V600E or MLH1 promoter methylation, the evidence includes a few case series. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. Studies have shown, with high sensitivity and specificity, an association between BRAF V600E variant and MLH1 promoter methylation with sporadic CRC. Therefore, this type of testing could eliminate the need for further genetic testing or counseling for Lynch syndrome. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who (1) are suspected of juvenile polyposis syndrome (JPS) or Peutz-Jeghers syndrome (PJS) or (2) are at-risk relatives of patients suspected of or diagnosed with JPS or PJS who receive genetic testing for SMAD4, BMPR1A, or STK11 genes, the evidence includes multiple observational studies. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. Studies have shown, with high sensitivity and specificity, an association between SMAD4, BMPR1A, or STK11 variants with JPS and PJS,

respectively. Direct evidence of clinical utility for genetic testing of a JPS or PJS is not available. Genetic testing may have clinical utility by avoiding burdensome and invasive endoscopic examinations, release from intensified screening programs resulting in psychological relief, and may improve health outcomes by identifying currently unaffected at-risk family members who require intense surveillance or prophylactic colectomy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

CLINICAL INPUT RECEIVED THROUGH PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

While the various Physician Specialty Societies and Academic Medical Centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the Physician Specialty Societies or Academic Medical Centers, unless otherwise noted.

In response to requests, Blue Cross Blue Shield Association (BCBSA) received input through three Physician Specialty Societies and three Academic Medical Centers while this policy was under review for October 2009. In general, those providing input were in agreement with the overall approach described in this policy.

PRACTICE GUIDELINES AND POSITION STATEMENTS

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Gastroenterology

The American College of Gastroenterology (2015) issued practice guidelines for the management of patients with hereditary gastrointestinal cancer syndromes.(26)

For Lynch syndrome, the College recommended:

“All newly diagnosed colorectal cancers (CRCs) should be evaluated for mismatch repair [MMR] deficiency.

Analysis may be done by immunohistochemical [IHC] testing for the MLH1/MSH2/MSH6/PMS2 proteins and/or testing for microsatellite instability [MSI]. Tumors that demonstrate loss of MLH1 should undergo BRAF testing or analysis for MLH1 promoter hypermethylation.

Individuals who have a personal history of a tumor showing evidence of MMR deficiency (and no demonstrated BRAF variant or hypermethylation of MLH1), a known family variant

associated with LS [Lynch syndrome], or a risk of $\geq 5\%$ chance of LS based on risk prediction models should undergo genetic evaluation for LS.(80)

Genetic testing of patients with suspected LS should include germline variant genetic testing for the MLH1, MSH2, MSH6, PMS2, and/or EPCAM genes or the altered gene(s) indicated by IHC testing.”

For adenomatous polyposis syndromes, the College recommended:

“Familial adenomatous polyposis (FAP)/MUTYH-associated polyposis/attenuated polyposis

Individuals who have a personal history of >10 cumulative colorectal adenomas, a family history of one of the adenomatous polyposis syndromes, or a history of adenomas and FAP-type extracolonic manifestations (duodenal/ampullary adenomas, desmoid tumors, papillary thyroid cancer, congenital hypertrophy of the retinal pigment epithelium, epidermal cysts, osteomas) should undergo assessment for the adenomatous polyposis syndromes.

Genetic testing of patients with suspected adenomatous polyposis syndromes should include APC and MUTYH gene variant analysis.”

For juvenile polyposis syndrome, the College recommended:

“Genetic evaluation of a patient with possible JPS [juvenile polyposis syndrome] should include testing for SMAD4 and BMPR1A mutations”

“Surveillance of the gastrointestinal (GI) tract in affected or at-risk JPS patients should include screening for colon, stomach, and small bowel cancers (strong recommendation, very low quality of evidence).

Colectomy and ileorectal anastomosis or proctocolectomy and ileal pouch-anal anastomosis is indicated for polyp-related symptoms, or when the polyps cannot be managed endoscopically (strong recommendation, low quality of evidence).

Cardiovascular examination for and evaluation for hereditary hemorrhagic telangiectasia should be considered for SMAD4 mutation carriers (conditional recommendation, very low quality of evidence).”

For Peutz-Jeghers syndrome, the College recommended:

“Genetic evaluation of a patient with possible PJS [Peutz-Jeghers syndrome] should include testing for STK11 mutations.”

“Surveillance in affected or at-risk PJS patients should include monitoring for colon, stomach, small bowel, pancreas, breast, ovary, uterus, cervix, and testes cancers. Risk for lung cancer is increased, but no specific screening has been recommended. It would seem wise to consider annual chest radiograph or chest computed tomography (CT) in smokers (conditional recommendation, low quality of evidence).”

American Society of Clinical Oncology and Society of Surgical Oncology

The American Society of Clinical Oncology (2015) concluded the European Society for Medical Oncology clinical guidelines published in 2013 were based on the most relevant scientific evidence and therefore endorsed them with minor qualifying statements (in bold italics).(81) The recommendations as related to genetic testing hereditary CRC syndromes are summarized below:

- “Tumor testing for **DNA MMR deficiency** with IHC for MMR proteins and/or MSI should be assessed in all CRC patients. As an alternate strategy, tumor testing should be carried out in individuals with CRC younger than 70 years, or those older than 70 years who fulfill any of the revised Bethesda guidelines.
- If loss of MLH1/PMS2 **protein expression** is observed in the tumor, analysis of BRAF V600E mutation or analysis of methylation of the MLH1 promoter should be carried out first to rule out a sporadic case. **If tumor is MMR deficient and somatic BRAF mutation is not detected or MLH1 promoter methylation is not identified, testing for germline mutations is indicated.**
- If loss of any of the other proteins (MSH2, MSH6, PMS2) is observed, germline genetic testing should be carried out **for the genes corresponding to the absent proteins (eg, MSH2, MSH6, EPCAM, PMS2, or MLH1).**
- Full germline genetic testing for **Lynch syndrome** should include DNA sequencing and large rearrangement analysis.
- Patients with multiple colorectal adenomas should be considered for full germline genetic testing of APC and/or MUTYH.
- Germline testing of MUTYH can be initiated by screening for the most common mutations (G396D, Y179C) in the white population followed by analysis of the entire gene in heterozygotes. Founder mutations among ethnic groups should be taken into account. **For nonwhite individuals, full sequencing of MUTYH should be considered.”**

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines on genetic/familial high-risk colorectal cancer syndromes (v.3.2024) are summarized in Table 2.(31)

Table 2. Criteria for Evaluation of Lynch Syndrome

| Criteria for the Evaluation of Lynch Syndrome |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Known LS pathogenic variant in the family |
| An individual with a LS related-cancer and any of the following: Diagnosed <50 y Another synchronous or metachronous LS-related cancer ^a regardless of age 1 first-degree or second-degree relative with LS-related ^a cancer diagnosed <50 y ≥2 first-degree or second-degree relatives with LS-related ^a cancers regardless of age |
| Personal history of a tumor with MMR deficiency determined by PCR, NGS, or IHC diagnosed at any age ^b |

Family history (on the same side of the family) of any of the following:
≥1 first-degree relative with colorectal or endometrial cancer diagnosed <50 y
≥1 first-degree relative with colorectal or endometrial cancer and another synchronous or metachronous LS-related cancer^a
≥2 first-degree or second-degree relatives with LS-related cancer,^a including ≥1 diagnosed <50 y
≥3 first-degree or second-degree relatives with LS-related cancers,^a regardless of age

An individual with a ≥5% risk of having an MMR gene pathogenic variant based on predictive models (ie, PREMM₅, MMRpro, MMRpredict)
Individuals with a personal history of CRC and/or endometrial cancer with a PREMM₅ score of ≥2.5% should be considered for MGPT.
For individuals without a personal history of CRC and/or endometrial cancer, some data have suggested using a PREMM₅ score threshold of ≥2.5% rather than ≥5% to select individuals for MMR genetic testing. Based on these data, it is reasonable for testing to be done based on the ≥2.5% score result and clinical judgment. Of note, with the lower threshold, there is an increase in sensitivity, but a decrease in specificity.

CRC: colorectal cancer; IHC: immunohistochemistry; LS: Lynch syndrome; MGPT: multi-gene panel testing; MMR: mismatch repair; MSI: microsatellite instability; NGS: next generation sequencing; PCR: polymerase chain reaction.

^a LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreas, urothelial, brain (usually glioblastoma), biliary tract, and small intestinal cancers, as well as sebaceous carcinomas, and keratoacanthomas as seen in Muir-Torre syndrome.

^b The NCCN recommends tumor screening for MMR deficiency for all CRC and endometrial cancers regardless of age at diagnosis. Tumor screening for CRCs for MMR deficiency for purposes of screening for LS is not required if MGPT is chosen as the strategy for screening for LS, but may still be required for CRC therapy selection. Consider tumor screening for MMR deficiency for sebaceous neoplasms as well as the following adenocarcinomas: small bowel, ovarian, gastric, pancreas, biliary tract, brain, bladder, urothelial, and adrenocortical cancers regardless of age at diagnosis. Direct referral for germline testing to rule out LS may be preferred in patients with a strong family history or if diagnosed prior to age 50 y, MSI-H, or loss of MMR protein expression. For patients aged ≥50 at CRC diagnosis, the panel has also recommended to consider germline MGPT evaluation for LS and other hereditary cancer syndromes.

Genetic Testing Recommendations for Lynch Syndrome

Screening of the tumor for defective DNA mismatch repair (MMR) using immunohistochemistry (IHC) and/or microsatellite instability (MSI) is used to identify which patients should undergo mutation testing for Lynch syndrome. (77) The NCCN guidelines also indicate that *BRAF* V600E testing or *MLH1* promoter methylation testing may be used when *MLH1* is not expressed in the tumor on immunohistochemical analysis to exclude a diagnosis of Lynch syndrome.

The NCCN guidelines for colon cancer (v.1.2025) recommend that all newly diagnosed patients with colon cancer be tested for mismatch repair (MMR) or microsatellite instability (MSI). (78)

The NCCN guidelines for uterine neoplasm (v.2.2025) also recommend universal screening for MMR genes. (77) Additionally, NCCN guidelines recommend screening for Lynch syndrome in all endometrial cancer patients younger than 50 years.

The NCCN guidelines for genetic/familial high-risk assessment: colorectal (v.1.2025) recommend genetic testing for at-risk family members of patients with positive variants in *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*.(78) These guidelines also address familial

adenomatous polyposis (classical and attenuated) and *MUTYH*-associated polyposis and are consistent with the information provided in this evidence review.

Surveillance Recommendations for Lynch Syndrome

The NCCN guidelines for colon cancer (v.1.2025) (78) and for CRC screening (v.1.2024) (79) recommend CRC patients treated with curative-intent surgery undergo surveillance colonoscopy at 1-year post-surgery and, if normal, again in 3-years, then every 5-years based on findings.

The NCCN guidelines on genetic/familial high-risk assessment for colorectal indicate for *MLH1*, *MSH2*, and *EPCAM* variant carriers that surveillance with colonoscopy should begin “at age 20 to 25 years or 2 to 5 years before the earliest colon cancer if it is diagnosed before age 25 years and repeat every 1 to 2 years.”(31)

MSH6 and *PMS2* variant carriers should begin surveillance with colonoscopy "at age 30 to 35 years or 2 to 5 years before the earliest colon cancer if it is diagnosed before age 30 years and repeat every 1 to 3 years" (31).

Peutz-Jeghers Syndrome and Juvenile Polyposis Syndrome

There are limited data on the efficacy of various screening modalities in juvenile polyposis syndrome and Peutz-Jeghers syndrome. The NCCN cancer risk and surveillance 2 category 2A recommendations for these are summarized in Tables 3 and 4. (31)

Table 3. Risk and Surveillance Guidelines for Peutz-Jeghers Syndrome

| Site | Lifetime Risk, % | Screening Procedure and Interval | Approximate Initiation Age, y |
|-----------------|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| Breast | 32 to 54 | Mammogram and breast MRI annually Clinical breast exam every 6 mo | 30 y |
| Colon | 39 | Colonoscopy every 2 to 3 y; shorter intervals may be indicated based on polyp size, number, and pathology | 18 y |
| Stomach | 29 | Upper endoscopy every 2 to 3 y; shorter intervals may be indicated based on polyp size, number, and pathology | 18 y |
| Small intestine | 13 | Small bowel visualization (CT or MRI enterography or video capsule endoscopy) every 2 to 3 y ;shorter intervals may be indicated based on polyp size, number, and pathology | 18 y |
| Pancreas | 11 to 36 | Annual imaging of the pancreas with either EUS or MRI/MRCP (both ideally performed at center of expertise) | 30 to 35 y |

| | | | |
|-----------------------------------------------------|---------|-----------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| Cervix (typically minimal deviation adenocarcinoma) | ≥10 | Pelvic examination and Pap smear annually Consider total hysterectomy (including uterus and cervix) once completed with childbearing | 18 to 20 y |
| Uterus | 9 | Annual pelvic examination with endometrial biopsy if abnormal bleeding | 18 to 20 y |
| Ovary (sex cord tumor with annular tubules) | ≥20 | Annual pelvic examination with annual pelvic ultrasound | 18 to 20 y |
| Lung | 7 to 17 | Provide education about symptoms and smoking cessation No other specific recommendations have been made | |
| Testes (Sertoli cell tumors) | 9 | Annual testicular exam and observation for feminizing changes | Continued from pediatric screening |

CT: computed tomography; EUS: endoscopic ultrasound; MR: magnetic resonance; MRCP: Magnetic resonance cholangiopancreatography; MRI: magnetic resonance imaging.

^aBased on clinical judgment, early initiation age may be considered, such as 10 y younger than the earliest age of onset in the family.

Table 4. Pediatric and Adult Risk and Surveillance Guidelines for Juvenile Polyposis Syndrome

| Site | Lifetime Risk, % for SMAD4/BMP1A variants | Screening Procedure and Interval | Approximate Initiation Age, y |
|-----------------|---------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|
| Colon | up to 50 | Adults: Colonoscopy every 1–3 years. Intervals should be based on polyp size, number, and pathology ^a Pediatrics: Colonoscopy every 2–3 years. Intervals should be based on polyp size, number, and pathology ^a | Adults: 18 y Pediatric: 12-15 y |
| Stomach | up to 21, especially if multiple gastric polyps present | Adults: Upper endoscopy every 1–3 years. Intervals should be based on polyp size, number, and pathology. ^{a,b} Pediatrics: Upper endoscopy and polypectomy every 2–3 years. Intervals should be based on polyp size, number, and pathology ^a | Adults: 18 y Pediatric: 12-15 y |
| Small intestine | Rare, undefined | No recommendations made | |
| HHT | 22 | In individuals with SMAD4 variants, screen for vascular lesions associated with HHT | Within first 6 mo of life, or at time of diagnosis |

HHT: hereditary hemorrhagic telangiectasia.

^a If polyp burden or polyp-related symptoms (ie, anemia) cannot be controlled endoscopically or prevent optimal surveillance for cancer, consideration should be given to gastrectomy and/or colectomy.

^b While SMAD4 pathogenic variant carriers often have severe upper gastrointestinal tract involvement, BMP1A pathogenic variant carriers may have a less severe upper gastrointestinal tract phenotype and may merit lengthened surveillance intervals in the absence of polyps. Gastric cancer risk for BMP1A pathogenic variant carriers may be lower than for SMAD4 pathogenic variant carriers

US Multi-Society Task Force on Colorectal Cancer

According to the US Multi-Society Task Force, Septin9 is not recommended for colorectal cancer screening.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 11.

Table 5. Summary of Key Trials

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|----------------|------------------------------------------------------------------------------------------------|--------------------|-----------------|
| Ongoing | | | |
| NCT02494791 | Universal Screening for Lynch Syndrome in Women With Endometrial and Non-Serous Ovarian Cancer | 886 | July 2025 |
| NCT04494945 | Approaches to Identify and Care for Individuals With Inherited Cancer Syndromes | 27500 | Jun 2030 |

NCT: national clinical trial.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

No U.S. Preventive Services Task Force recommendations for genetic testing of Lynch syndrome and other inherited colon cancer syndromes have been identified.

Government Regulations National:

Under Medicare, genetic tests for cancer are a covered benefit only for a beneficiary with a personal history of an illness, injury, or signs/symptoms thereof (i.e. clinically affected). A person with a personal history of a relevant cancer is a clinically affected person, even if the cancer is considered cured. Predictive or pre-symptomatic genetic tests and services, in the absence of past or present illness in the beneficiary, are not covered under national Medicare rules. CMS recognizes Lynch syndrome as “an autosomal dominant syndrome that accounts for about 3-5% of colorectal cancer cases. [Lynch] syndrome variants occur in the following genes: *hMLH1*, *hMSH2*, *hMSH6*, *PMS2* and *EPCAM*.” The Centers for Medicare & Medicaid Services (CMS) also recognizes FAP and MAP syndromes and their associated variants.

Local:

WPS: L37224 MoIDX: APC and MUTYH Gene Testing

Original Effective date: 09/16/17; Revision Date: For services performed on or after 04/01/21, Retired 08/20/22

This policy provides Medicare coverage for APC and MUTYH gene testing for individuals suspected to have Familial Adenomatous Polyposis (FAP), Attenuated FAP (AFAP) or MYH-associated polyposis (MAP) with a personal history of ≥ 20 adenomas over a lifetime.

WPS: L36793 MoIDX: Genetic Testing for Lynch Syndrome

Original Effective Date: 2/16/17; Revision Date: For services performed on or after 2/25/21, Retired 08/20/22

This policy limits **LYNCH SYNDROME** (LS) genetic testing to a stepped approach for Microsatellite Instability and Immunohistochemistry (MSI/IHC) screening, *BRAF* gene mutation,

MLH1 gene promoter hypermethylation and targeted mismatch repair (MMR) germ-line gene testing to all patients with colorectal cancer (CRC) and endometrial cancer regardless of age, or a multi-gene NGS or other multi-analyte methodology that is inclusive of MSI microsatellite loci, and *MLH1*, *MSH2*, *MSH6* and *PMS2* genes. MSI/MMR testing is also covered for adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan.

Indications of Coverage

IHC and/or MSI Testing

LS tumor screening with IHC or MSI is considered medically necessary and covered by Medicare for the following indications:

- All individuals with colorectal cancer regardless of age **OR**
- Individuals with endometrial cancer
- *Hereditary nonpolyposis colorectal cancer (HNPCC)-related tumors include colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastomas as seen in Turcot syndrome), small intestinal cancers, and sebaceous gland adenomas and keratoacanthomas as seen in Muir-Torre syndrome.
- For patients with unresectable or metastatic solid tumors, either MSI or IHC or a multigene NGS or other multi-analyte methodology panel inclusive of MSI microsatellite loci, and *MLH1*, *MSH2*, *MSH6* and *PMS2* genes is medically reasonable and necessary.

For coverage, the treating physician/pathologist is expected to follow the stepped approach outlined for LS screening and targeted MMR testing in this policy. Germ-line testing includes sequence and duplication-deletion analysis for a given gene.

MMR Germline Gene Mutation Testing Exception

If a lab is unable to perform the stepped testing approach outlined in this LCD, multiple germ-line gene testing will be covered by Medicare only for one or more of the following findings:

- MSI/IHC testing yields normal IHC and MSI-H, suggesting LS
- If tumor is not available or determined by a pathologist to be inadequate to assess DNA MMR deficiency by MSI or IHC, then MMR germ-line testing can be conducted on blood from patient with CRC or endometrial cancer.
- Diagnosis of any Lynch-associated cancer prior to Medicare eligibility AND tumor sample no longer available AND meets either Revised Bethesda guidelines or has at least a personal 5% estimated likelihood to be mutation positive, as calculated by an established available risk model (e.g., PREMM, MMRpredict, MMRpro).

If targeted gene testing is not possible, testing of the four MMR genes can be performed concurrently followed by testing for *EPCAM*, or per a testing strategy deemed appropriate by the physician.

Testing for Known Familial Variant

Testing for a specific known familial variant is considered medically necessary and covered only when the individual being tested has signs and symptoms of a Lynch-associated cancer AND has a blood relative with the specific disease-causing mutation for LS.

Note: This LCD does not imply that testing family members of a known familial variant is not

medically warranted. The scope of the Medicare benefit requires the beneficiary to have signs and symptoms of disease. Coverage of molecular testing for LS for carrier status or family studies is considered screening and is statutorily excluded from coverage.

Limitations

Molecular testing for LS to identify carrier status or family studies is not a Medicare benefit.

WPS: L36805 Special Histochemical Stains and Immunohistochemical Stains

Original Effective Date: For services performed on or after 2/16/17, Revision effective date 09/29/22

Medical Necessity of Services Performed

There are many different relationships that exist in providing the provision of pathology services in the United States. Some physicians, groups, laboratories and hospitals submit global claims for the services described in this policy. In other instances, there are separate individuals or entities providing the professional (-26) and the technical services (-TC). It is the obligation of each billing party to recognize that they are responsible for the medical necessity of the charges submitted. For example, when a physician or physician group bills for the professional component of services described in this policy and another entity bills for the technical services, it is the obligation of each entity to independently assure the medical necessity of the services rendered and billed.

Special Stains/IHC Medical Necessity

The *CMS Internet-Only Manual, Pub. 100-02, Medicare Benefit Policy Manual* (Chapter 15, §80.6.5) specifies “...there may be additional tests, such as special stains, that the pathologist may need to perform, even though they have not been specifically requested by the treating physician/practitioner. The pathologist may perform such additional tests under the following circumstances:

- Services are **medically necessary** so that a complete and accurate diagnosis can be reported to the treating physician/practitioner;
- **Results** of the tests are communicated to and are used by the treating physician/practitioner in the treatment of the beneficiary; and
- Pathologist **documents** in his/her report **why** additional testing was done.”

Special Stains and/or IHC for GI Pathology

Lynch Syndrome tumor screening for DNA mismatch repair (MLH1, MSH2, MSH6 and PMS2) by qualitative IHC and/or microsatellite instability (MSI) is considered medically necessary and covered by Medicare for the following indications:

- All individuals with colorectal cancer diagnosed at age ≤70 years of age, and those > 70 years of age who meet the revised Bethesda guidelines **OR**
- Individuals with endometrial cancer

No definitive algorithm for LS screening has been recommended. However, if IHC is done first and is abnormal, MSI testing is not warranted. If IHC is normal, MSI may be warranted. IHC testing **LYNCH SYNDROME** is qualitative and does not require the use of tumor morphometry.

WPS: Local Coverage Article – A55135 “MoIDX: Billing and Coding for Lynch Syndrome Testing Services”

Original Effective Date: 2/16/17, Revision effective date 10/01/21, **Retired 08/20/22**

As per the LCD MoIDX: Genetic Testing for **LYNCH SYNDROME** (LS), laboratory providers must follow a stepped approach to meet the reasonable and necessary criteria. To progress to each subsequent step, refer to the indications detailed in the policy.

Step 1:

LS screening to detect the presence of a defective mismatch pair may be performed by ONE or both of the following methods:

1. Immunohistochemistry (IHC) for MLH1, MLH2, MSH6, and PMS2
2. Microsatellite instability analysis (MSI)

To bill services for this step, choose the appropriate codes for method(s) performed:

| | Test | CPT Code | Units of Service (UOS) |
|-----------------|---------------|----------|------------------------|
| Method 1 | IHC-initial | 88342 | 1 |
| | IHC-ea. Addl. | 88341 | 3 |
| AND/OR | | | |
| Method 2 | MSI | 81301 | 1 |

If results from methods 1 or 2 are abnormal, proceed to step 2.

Step 2:

LS definitive testing may be performed by ONE of the following methods:

1. Next generation sequencing (NGS or "hotspot") testing platforms, OR
2. Non-NGS testing platforms

To bill services for this step, choose ONE method:

| | Test | CPT Code | Units of Service (UOS) |
|---------------------------|----------------------------------------------------------|----------|------------------------|
| Step 2 Method 1 | Hereditary colon cancer disorders genomic sequence panel | 81435 | 1 |
| OR | | | |
| Step 2 Method 2 | Non-NGS testing: Continue steps as indicated by LCD | | |
| Step 3 | BRAF V600E | 81210 | 1 |
| Step 4 | MLH1, Promoter Methylation | 81288 | 1 |
| Step 5A | MLH1 | 81292 | 1 |
| | | 81293 | 1 |
| | | 81294 | 1 |
| Step 5B | MLH2 | 81295 | 1 |
| | | 81296 | 1 |
| | | 81297 | 1 |
| Step 5C | MLH6 | 81298 | 1 |
| | | 81299 | 1 |
| | | 81300 | 1 |
| Step 5D | PMS2 | 81317 | 1 |

| | | | |
|--------|-------|-------|---|
| | | 81318 | 1 |
| | | 81319 | 1 |
| Step 6 | EpCAM | 81403 | 1 |

Note: For Non-NGS testing (Step 2-6, Method 2), you may ONLY progress to the subsequent genetic test **IF** additional information is necessary to rule out or diagnose LS

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Somatic Biomarker Testing (including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer (KRAS, NRAS, BRAF, MMR/MSI, HER2, and TMB)
- Analysis of Human FIT-DNA (i.e., ColoGuard®) in Stool Samples as a Technique for Colorectal Cancer Screening

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through February 2025, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

| Policy Effective Date | BCBSM Signature Date | BCN Signature Date | Comments |
|-----------------------|----------------------|--------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 5/1/02 | 5/1/02 | 5/1/02 | Joint policy established |
| 10/6/03 | 10/6/03 | 10/14/03 | Routine maintenance |
| 1/1/07 | 10/31/06 | 11/19/06 | Routine Maintenance |
| 1/1/08 | 10/16/07 | 11/11/07 | Routine Maintenance |
| 1/1/09 | 10/13/08 | 10/13/08 | Maintenance-another genetic test added |
| 7/1/09 | 4/21/09 | 4/21/09 | Criteria clarified |
| 9/1/11 | 6/21/11 | 6/21/11 | Routine Maintenance; "Lynch syndrome" verbiage added to policy in place of HNPCC; Medical Policy Statement revised for clarity; background section updated; Medicare section updated; added "Immunohistochemistry" to title; updated Bethesda and Amsterdam guidelines |
| 5/1/12 | 2/21/12 | 2/21/12 | New codes added for 2012; deleted S codes pertaining to Lynch syndrome testing; inclusion criteria revised to reduce ambiguity; <i>PMS2</i> and <i>EPCAM</i> testing added to policy |
| 11/1/12 | 8/21/12 | 8/21/12 | Clarification made to inclusion criteria, section C, fourth bullet. |
| 7/1/13 | 4/22/13 | 4/22/13 | New codes 81201-81203, 81401 and 81406 added for 2013; title changed from "Genetic Testing for Inherited Susceptibility to Colon Cancer, |

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| | | | Including Microsatellite Instability and Immunohistochemistry Testing” to current title; In Section C of the Inclusion section, added criteria for patients with endometrial cancer and one first-degree relative diagnosed with a Lynch-associated cancer; in Section E of the Inclusion section, added genes “ <i>MLH1</i> , <i>PMS2</i> , and <i>MSH6</i> ” in addition to <i>MSH2</i> . |
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| 11/1/13 | 8/20/13 | 9/5/13 | Added clarifying statement to Inclusion sections C and E: “In cases when testing is proposed for an individual without a personal history of colorectal cancer, the Revised Bethesda criteria would be applicable <u>to that individual’s first- and/or second-degree relatives</u> ”; In Section D in the Inclusion section, added criterion “Patients with endometrial cancer and one first-degree relative diagnosed with a Lynch-associated cancer, for the diagnosis of Lynch syndrome”. |
| 3/1/15 | 12/9/14 | 12/29/14 | Routine maintenance; deleted codes S3833 and S3834; added 81403 for <i>EPCAM</i> testing; added 81210 for <i>BRAF V600E</i> testing; added 81288 for <i>MLH1</i> promoter methylation testing; added 81435 and 81436; updated MPS and Inclusion criteria to include <i>BRAF V600E</i> testing; revised MPS to reflect broader scope of tests; added LCD information. |
| 7/1/16 | 4/19/16 | 4/19/16 | Routine maintenance |
| 11/1/16 | 8/16/16 | 8/16/16 | Routine maintenance |

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|---------|---------|---------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 11/1/17 | 8/15/17 | 8/15/17 | <ul style="list-style-type: none"> • Routine maintenance. • References added. • Added 2.2016 NCCN criteria to position statements: “<i>Consider</i> testing individuals with $\geq 5\%$ risk of Lynch syndrome on one of the following variant prediction models: MMRpro, PREMM_{1,2,6}, or MMRpredict. Testing affected individuals in the family with an LS-related cancer is preferred.” • Title changed from...”other inherited intestinal polyposis” to “other inherited colon cancers” |
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| 3/1/18 | 12/12/17 | 12/12/17 | <ul style="list-style-type: none"> • Routine maintenance • Code 81528 (aligning with CRC policy regarding Cologuard) and 81327 added to noncovered • FDA approval and exclusions for Cologuard added • US Multi-Task Force exclusion of Septin9 added • Updated LCDs |
| 3/1/19 | 12/11/18 | | <ul style="list-style-type: none"> • Routine maintenance • Added juvenile polyposis syndrome and Peutz-Jeghers syndrome indications. • Inclusions added for genetic testing for SMAD4, BMPR1A, or STK11 gene variants |
| 7/1/19 | 4/16/19 | | <ul style="list-style-type: none"> • Routine maintenance |
| 7/1/20 | 4/14/20 | | <ul style="list-style-type: none"> • Routine maintenance • Updated inclusions for MMR and EPCAM gene testing to include “documentation of 5% or higher predicted risk of the syndrome on a risk prediction model” for coverage • Incorporated first- and second-degree relatives into “at risk” |
| 7/1/21 | 4/20/21 | | <ul style="list-style-type: none"> • Routine maintenance • References on NCCN updated |

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| | | | <ul style="list-style-type: none"> • Peutz-Jeghers syndrome updated with revised NCCN diagnostic criteria. • No change in Medical Policy Statement • Code update team identified code 0238U – added this code to other codes: investigational, not medically necessary, etc. • Removed 81528 (Cologuard) from the policy on the Regulatory Section removed 81528 from under Other Codes: (investigational, not medically necessary, etc.), and added the Analysis of Human DNA in Stool Samples as a Technique for CRC policy on the related policies section. |
| 7/1/22 | 4/19/22 | | <p>Routine Maintenance</p> <p>Under Inclusions and Exclusions: Under MMR gene testing clarified "with tumor testing suggesting germline MMR deficiency or meeting clinical criteria for Lynch syndrome"; the intent of the policy is unchanged.</p> <p>Under exclusions policy statements added that all other situations are considered experimental/investigational.</p> <p>In the Background section, diagnostic criterion for Juvenile Polyposis Syndrome was updated from "3 to 5 juvenile polyps in the colon" to "at least 5 juvenile polyps in the colon", updated Inclusions section under SMAD4 and BMPR1A to reflect this correction.</p> <p>Table 4 revised to include both pediatric and adult risk and surveillance guidelines for juvenile polyposis syndrome. References on NCCN updated and references added</p> |
| 7/1/23 | 4/18/23 | | <p>Routine Maintenance.</p> <p>References on NCCN updated and reference added.</p> |

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| | | | Vendor: NA (ky) |
| 7/1/24 | 4/16/24 | | Routine Maintenance. References on NCCN updated Vendor: NA (ky) |
| 7/1/25 | 4/15/25 | | Routine Maintenance. Code 81436 deleted eff 12/31/24; 81435 revised 1/1/25. References on NCCN updated. Vendor: NA (ky) |

Next Review Date: 2nd Qtr, 2026

Pre-Consolidation Medical Policy History

| Original Policy Date | Comments |
|----------------------|--------------|
| BCN: 3/14/01 | Revised: N/A |
| BCBSM: N/A | Revised: N/A |

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR LYNCH SYNDROME AND OTHER INHERITED COLON
CANCER SYNDROMES

I. Coverage Determination:

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| Commercial HMO (includes Self-Funded groups unless otherwise specified) | Covered, policy guidelines apply |
| BCNA (Medicare Advantage) | Refer to Medicare information under the Governmental Regulations section of this policy. |
| BCN65 (Medicare Complementary) | Coinsurance covered if primary Medicare covers the service. |

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.