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

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DESCRIPTION:

There are currently 2 well-defined types of hereditary colorectal cancer (CRC), familial adenomatous polyposis (FAP) and Lynch syndrome (formerly hereditary nonpolyposis CRC).

Familial Adenomatous Polyposis (FAP) and Associated Variants

FAP typically develops by age 16 years and can be identified by the appearance of hundreds to thousands of characteristic, pre-cancerous colon polyps. If left untreated, all affected individuals will develop colorectal cancer. The mean age of colon cancer diagnosis in untreated individuals is 39 years. FAP accounts for about 1% of colorectal cancer.

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 subset of FAP patients may have an attenuated form of FAP, typically characterized by fewer than 100 cumulative colorectal adenomas occurring later in life than in classical FAP. CRC occurs at an average of 50-55 years, but lifetime risk of CRC remains high (about 70% by age 80). 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 similar 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.

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. 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 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.

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 rare, with an estimated incidence of 1 in 100,000 to 160,000. Generalized JPS refers to polyps in the upper and lower gastrointestinal tract, and juvenile polyposis coli refers to polyps of the colon and rectum. Those with JPS are at a higher risk for CRC and gastric cancer.

Summary and Analysis of Evidence: Patients suspected of attenuated FAP, MAP, and Lynch syndrome who receive genetic testing for APC, or are at-risk relatives of patients with FAP who receive genetic testing for MUTYH after a negative APC test result, the evidence includes a TEC Assessment. 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 2 leads to different management strategies. Depending on the 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. Patients suspected of attenuated FAP, MAP, and Lynch syndrome, have colon cancer, have endometrial cancer meeting clinical criteria for Lynch syndrome, are at-risk relatives of patients with Lynch syndrome, are without colon cancer but with a family history meeting 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 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 CRC. 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 followed 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. Patients 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. 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. Patients who have CRC in whom MLH1 protein is not expressed on immunohistochemical (IHC) analysis and who receive genetic testing for BRAF V600E or MLH1 promoter methylation, the evidence includes case series. 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. Patients who are suspected of JPS or PJS or are at-risk relatives of patients suspected of or diagnosed with JPS or Peutz-Jeghers syndrome (PJS) who receive genetic testing for SMAD4, BMPR1A, or STK11 genes, respectively, the evidence includes multiple observational studies. Studies have shown, with high sensitivity and specificity, an association between SMAD4 and BMPR1A and STK11 variants with JPS and PJS, respectively. Direct evidence of clinical utility for genetic testing of 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 improving 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.

POSITION STATEMENT:

NOTE: Coverage for genetic testing, screening, and counseling are applicable only under those contracts that include benefits for genetic testing, preventive health services, screening services, and medical counseling. Coverage may be governed by state or federal mandates.

APC Testing

Genetic testing for APC gene variants **meets the definition of medical necessity** for one of the following:

1. At-risk relatives (eg. First-degree relatives; or in the case of a small family pedigree when extended family members may need to be included in the testing strategy) of members with familial adenomatous polyposis (FAP) and/or a known APC variant.
2. Members with a differential diagnosis of attenuated FAP versus MUTYH-associated polyposis (MAP) versus Lynch syndrome.

Genetic testing for APC gene variants **does not meet the definition of medical necessity** for members with colorectal cancer with classical FAP for confirmation of the FAP diagnosis. The testing has no role in the evaluation, diagnosis, or treatment of members where the diagnosis and treatment are based on the clinical presentation.

Testing for germline APC gene variants for inherited CRC syndromes is considered **experimental or investigational** in all other situations. There is insufficient clinical evidence to permit conclusions on net health outcomes.

MUTYH Testing

Genetic testing for MUTYH gene variants **meets the definition of medical necessity** in members with a differential diagnosis of attenuated FAP versus MAP versus Lynch syndrome and a negative result for APC gene variants. Family history of no parents or children with FAP is consistent with MAP (autosomal recessive).

Testing for germline MUTYH gene variants for inherited CRC syndromes is considered **experimental or investigational** in all other situations. There is insufficient clinical evidence to permit conclusions on net health outcomes.

MMR Gene Testing

Genetic testing for MMR genes (MLH1, MSH2, MSH6, PMS2) **meets the definition of medical necessity** for one of the following:

1. Members with CRC with tumor testing suggesting germline MMR deficiency or meeting clinical criteria for Lynch syndrome.
2. Members with endometrial cancer with tumor testing suggesting germline MMR deficiency or meeting clinical criteria for Lynch syndrome.
3. At-risk relatives (eg. First-degree relatives; or in the case of a small family pedigree when extended family members may need to be included in the testing strategy) of members with Lynch syndrome with a known MMR gene variant.
4. Members with a differential diagnosis of attenuated FAP versus MAP versus Lynch syndrome.
5. Members without CRC 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 (ie. PREMM5[®], MMRpro, or MMRpredict), when no affected family members have been tested for MMR variants.

Testing for germline MMR gene variants for inherited CRC syndromes is considered **experimental or investigational** in all other situations. There is insufficient clinical evidence to permit conclusions on net health outcomes.

EPCAM Testing

Genetic testing for EPCAM gene variants **meets the definition of medical necessity** for one of the following:

1. Members with CRC, for the diagnosis of Lynch syndrome when:
 - Tumor tissue shows lack of MSH2 expression by immunohistochemistry and member is negative for a MSH2 germline variant; **OR**
 - Tumor tissue shows a high level of microsatellite instability and member is negative for a germline variant in MSH2, MLH1, PMS2, and MSH6.
2. At-risk relatives (eg. First-degree relatives; or in the case of a small family pedigree when extended family members may need to be included in the testing strategy) of members with Lynch syndrome with a known EPCAM variant; **OR**
3. Members without CRC 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 (ie. PREMM5, MMRpro, or MMRpredict), when no affected family members have been tested for MMR variants, and when sequencing for MMR variants is negative.

Testing for germline EPCAM gene variants for inherited CRC syndromes is considered **experimental or investigational** in all other situations. There is insufficient clinical evidence to permit conclusions on net health outcomes.

BRAF V600E or MLH1 Promoter Methylation

Genetic testing for BRAF V600E or MLH1 promoter methylation **meets the definition of medical necessity** to exclude a diagnosis of Lynch syndrome when the MLH1 protein is not expressed in a CRC tumor on immunohistochemical analysis.

Testing for somatic BRAF V600E or MLH1 promoter methylation to exclude a diagnosis of Lynch syndrome is considered **experimental or investigational** in all other situations. There is insufficient clinical evidence to permit conclusions on net health outcomes.

SMAD4 AND BMPR1A Testing

Genetic testing for SMAD4 and BMPR1A gene variants **meets the definition of medical necessity** when **ONE** of the following criteria is met:

1. Member has a clinical diagnosis of juvenile polyposis syndrome based on the presence of any **ONE** of the following:
 - at least 3 to 5 juvenile polyps in the colon
 - multiple juvenile polyps in other parts of the gastrointestinal tract
 - any number of juvenile polyps in a person with a known family history of juvenile polyps.
2. Member is an at-risk relative of an individual suspected of or diagnosed with juvenile polyposis syndrome.

Testing for germline SMAD4 and BMPR1A gene variants for inherited CRC syndromes is considered **experimental or investigational** in all other situations. There is insufficient clinical evidence to permit conclusions on net health outcomes.

STK11 Testing

Genetic testing for STK11 gene variants **meets the definition of medical necessity** when any **ONE** of the following criteria is met:

1. Member has a clinical diagnosis of Peutz-Jeghers syndrome based on the presence of any **2** of the following:
 - presence 2 or more histologically confirmed Peutz-Jeghers polyps of the gastrointestinal tract
 - characteristic mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, or fingers
 - family history of Peutz-Jeghers syndrome.

2. Member is an at-risk relative of an individual suspected of or diagnosed with Peutz-Jeghers syndrome.

Testing for germline STK11 gene variants for inherited CRC syndromes is considered **experimental or investigational** in all other situations. There is insufficient clinical evidence to permit conclusions on net health outcomes.

Other

Genetic testing for all other genes for an inherited CRC syndrome is considered **experimental or investigational**. There is insufficient clinical evidence to permit conclusions on net health outcomes.

Pre- and post test genetic counseling **meets the definition of medical necessity** as an adjunct to the genetic testing itself.

*** Amsterdam II Criteria**

Three or more relatives with Lynch syndrome associated cancers (CRC, cancer of the endometrium, small bowel, ureter or renal pelvis) and **ALL** of the following:

- One should be a first-degree relative of the other two; **AND**
- Two or more successive generations affected; **AND**
- One or more relatives diagnosed before age 50 years; **AND**
- Familial adenomatous polyposis (FAP) should be excluded in CRC cases; **AND**
- Tumors should be verified by pathologic examination.

Modifications: Either very small families, which cannot be further expanded, can be considered to have Lynch syndrome with only 2 CRCs in first-degree relatives if at least 2 generations have the cancer and at least 1 case of CRC was diagnosed by the age of 55 years; **OR** in families with 2 first-degree relatives affected by CRC, the presence of a third relative with an unusual early-onset neoplasm or endometrial cancer is sufficient.

***Revised Bethesda Guidelines:**

Member has cancer associated with Lynch syndrome (CRC, cancer of the endometrium, small bowel, ureter or renal pelvis) and **ANY** one of the following;

- CRC diagnosed in an individual younger than 50 years old; **OR**
- Presence of synchronous (at the same time) or metachronous (at another time, ie, a recurrence of) CRC or other Lynch syndrome-associated tumors**, regardless of age; **OR**
- CRC with high microsatellite instability histology diagnosed before 60 years old; **OR**
- CRC diagnosed in one or more first-degree relatives with a Lynch syndrome-associated tumor**, with one of the cancers being diagnosed before 50 years of age; **OR**
- CRC diagnosed in two or more first- or second-degree relatives with Lynch syndrome-related tumors** regardless of age.

** (Lynch syndrome-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.)

BILLING/CODING INFORMATION:

CPT Coding:

81201	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
81202	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
81203	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants
81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
81288	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g. hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81293	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g. hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81294	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g. hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81295	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g. hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81296	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g. hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81297	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g. hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81298	MSH6 (mutS homolog 6 [E. coli]) (e.g. hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81299	MSH6 (mutS homolog 6 [E. coli]) (e.g. hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81300	MSH6 (mutS homolog 6 [E. coli]) (e.g. hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81301	Microsatellite instability analysis (e.g. hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (e.g. BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
81317	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g. hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81318	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g. hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants

81319	PMS2 (postmeiotic segregation increased 2 [<i>S. cerevisiae</i>]) (e.g. hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81435	Hereditary colon cancer-related disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatous polyposis), genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants
96041	Medical genetics and genetic counseling services, each 30 minutes of total time provided by the genetic counselor on the date of the encounter

HCPCS Coding:

S0265	Genetic counseling, under physician supervision, each 15 minutes
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REIMBURSEMENT INFORMATION:

Services may be subject to medical review. The following information is required documentation to support medical necessity: reason for test(s), previous lab results, how the results of the test will be utilized, how the results of the test will contribute to improved health outcomes, or alters member's treatment and or management.

LOINC Codes:

Documentation Table	LOINC Codes	LOINC Time Frame Modifier Code	LOINC Time Frame Modifier Codes Narrative
Physician history and physical	28626-0	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim
Attending physician visit note	18733-6	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim.
Attending physician progress note	18741-9	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim.
Plan of treatment	18776-5	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim.
Laboratory studies	26436-6	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage products:

The following Local Coverage Determination (LCD) was reviewed on the last guideline reviewed date:
Genetic Testing for Lynch Syndrome (L34912) located at fcso.com.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at [Coverage Protocol Exemption Request](#).

DEFINITIONS:

First-degree relative: Parent, full-sibling, child.

Second-degree relative: Aunt, uncle, grandparent, grandchild, niece, nephew, half-sibling.

Third-degree relative: Great-grandparent, great-grandchild, great-aunt, great-uncle, first cousin, half-aunt, half-uncle.

RELATED GUIDELINES:

[Genetic Testing, 05-82000-28](#)

[Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers \(BRCA1, BRCA2, PALB2\), 05-82000-30](#)

[Somatic Biomarker Testing \(Including Liquid Biopsy\) for Targeted Treatment in Metastatic Colorectal Cancer \(KRAS, NRAS, BRAF, NTRK, and HER2\), 05-86000-28](#)

OTHER:

Validated risk prediction models are available online at:

- MMRpredict - webapps.igc.ed.ac.uk/world/research/hnpccpredict/
- MMRpro - www4.utsouthwestern.edu/breasthealth/cagene/
- PREMM5 - premm.dfci.harvard.edu.

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Medical Policy and Coverage Committee on 10/23/25.

GUIDELINE UPDATE INFORMATION:

11/15/03	Medical Coverage Guideline Annual review. Developed separate policy for Genetic Testing for Inherited Susceptibility to Colon Cancer Including Microsatellite Instability.
11/15/04	Revised description section. Revised coverage criteria based on the Amsterdam II criteria. Update references.
07/01/05	HCPCS update. Added S0265.
01/01/06	Annual HCPCS coding update: added 83900, 83907, 83908, 83909, and 83914. Revised 83898.
06/15/06	Revision to include new codes into limitation section.
10/15/06	Biennial review; investigational statement deleted; HNPPC coverage edited; coding information revised; categorized as NLR.
01/01/07	Annual HCPCS coding update: added 96040, deleted 99401, 99402, 99403, 99404.
08/15/07	Review, coverage statements maintained, guideline reformatted, references updated.
01/01/08	Annual HCPCS coding update: revised 83898, 83900, and 83908.
07/15/08	Annual review: position statements maintained, references updated.
01/01/09	Annual HCPCS coding update: descriptor updated for codes 83890, 83892, 83894, 83896, 83897, 83900, 83903, 83907, 83909, and 83914.
08/15/09	Annual review: position statements revised, description section and references updated.
10/15/09	Reimbursement section updated.
07/15/10	Annual review: position statements maintained and references updated.
10/01/11	Revision; formatting changes
01/01/12	Annual HCPCS update. Added codes 81292-81301, 81317-81319; revised Billing/Coding and Reimbursement Information sections.
04/01/12	Quarterly HCPCS update. Deleted codes S3828-S3831.
01/01/13	Annual HCPCS update. Added codes 81201-81203.
01/01/14	Annual HCPCS update. Deleted codes S3833-S3834. Program Exceptions section updated.
01/01/15	Annual HCPCS/CPT update. Added code 81288.
02/15/15	Review; description section, position statements, Medicare program exception, coding, and references updated; formatting changes.
01/01/16	Annual HCPCS/CPT update; code 81210 revised.

06/15/16	Review; guideline title, position statement section, Medicare program exception and references updated; formatting changes.
11/15/18	Review; Genetic testing for SMAD4, BMPR1A, or STK11 statements for juvenile polyposis syndrome and Peutz-Jeghers syndrome added; description section, position statement section, and references updated; formatting changes.
11/15/19	Revision; MMR & EPCAM testing criteria, description section, and references updated.
11/15/20	Review; Coverage maintained and references updated.
11/15/21	Review: Update position statements and references.
11/15/23	Review: Position statements maintained and references updated.
11/15/24	Review: Position statements maintained; description and references updated.
01/01/25	Annual CPT/HCPCS coding update. Code 96041 added.
11/15/25	Annual review: Position statements maintained; coding and references updated.