Genetic Testing: Inherited Susceptibility to Colorectal Cancer

MEDICAL POLICY NUMBER: 115

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INSTRUCTIONS FOR USE: Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Company reserves the right to determine the application of medical policies and make revisions to medical policies at any time. The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement. Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

SCOPE: Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

PLAN PRODUCT AND BENEFIT APPLICATION

☒ **Commercial** ☒ **Medicaid/OHP*** ☐ **Medicare****

*Medicaid/OHP Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

**Medicare Members

This *Company* policy may be applied to Medicare Plan members only when directed by a separate *Medicare* policy. Note that investigational services are considered **"not medically necessary"** for Medicare members.

COVERAGE CRITERIA

Notes:

- Genetic tests addressed in this policy only include the following well-defined inherited cancer syndromes:
  - Hereditary Non-Polyposis Colorectal Cancer (HNPCC, also known as Lynch Syndrome);
  - Familial Adenomatous Polyposis (FAP) and Attenuated FAP (AFAP);
  - MYH-associated Polyposis (MAP).
- Testing for additional, lower penetrant syndromes or genes are not addressed by this policy and may be subject to review by the policy, Genetic and Molecular Testing.
- This policy does not address immunohistochemistry (IHC) or microsatellite instability (MSI) tests, which may be considered medically necessary and standard of care in patients with colon or endometrial cancer.
- Both maternal and paternal family histories must be considered separately when identifying families with an increased risk of colorectal cancer.
- When possible, family members with cancer associated with inherited colorectal cancer should be tested first, prior to testing unaffected members. Testing an unaffected member has significant limitations on interpreting test results. Pre-test counseling notes should document the reason why an affected family member cannot be tested prior to testing an unaffected member.

Genetic Testing: Covered Testing

I. Genetic testing for a single gene or any combination of the following genes (*APC*, *MUTYH*, *MLH1, MSH2, MSH6, PMS2*, and/or *EPCAM*) may be considered **medically necessary** for the evaluation of high-risk colorectal cancer syndromes when Genetic Counseling general

requirements have been met [see Genetic Counseling (All Lines of Business Except Medicare) policy for specific criteria] **and any one** of the following criteria (A.-D.) are met:

A. Documentation indicates a first-degree relative* has a known pathogenic mutation in one of the genes listed above and testing is based on the identified mutation; **or**
B. Patient has a personal history of **any one** of the following (1.-6.):
    1. Greater than 10 adenomas; **or**
    2. Colorectal or endometrial cancer diagnosed <50 years; **or**
    3. Colorectal or endometrial cancer and another Lynch Syndrome (LS)-related cancer** (can be synchronous or metachronous); **or**
    4. Colorectal or endometrial cancer and one or more first- or second-degree relative(s) with an LS-related cancer diagnosed <50 years; **or**
    5. Colorectal or endometrial cancer and two or more first- or second-degree relatives with an LS-related cancer, regardless of age; **or**
    6. Colorectal or endometrial cancer at any age with tumor showing evidence of mismatch repair deficiency, either by microsatellite instability (MSI) or loss of MMR protein expression; **or**
C. Patient has a family history of **any one** of the following (1.-5.):
    1. One or more relative(s) with polyposis (greater than 10 adenomas); **or**
    2. One or more first-degree relative(s)* with colorectal or endometrial cancer diagnosed <50 years; **or**
    3. One or more first-degree relative(s)* with colorectal or endometrial cancer and another LS-related cancer**; **or**
    4. Two or more first- or second-degree relative(s)* with LS-related cancers, including one or more diagnosed <50 years; **or**
    5. Three or more first- or second-degree relative(s)* with LS-related cancers, regardless of age; **or**
D. An individual with a LS-related cancer or an unaffected individual with a ≥5% risk for having an MMR gene mutation based on one of the following prediction models: MMRpro, PREMM5, or MMRpredict. *** (See Policy Guidelines for links to tools.)

II. Genetic testing for *BRAF* V600E or *MLH1* promoter methylation testing is considered **medically necessary** to rule out a diagnosis of Lynch syndrome in patients with a loss of DNA protein expression of *MLH1* on IHC tumor testing or an MSI-H test result.

Genetic Testing: Non-covered Testing

III. Genetic testing for *APC, MUTYH, MLH1, MSH2, MSH6, PMS2* and/or *EPCAM* gene mutation(s) is considered **not medically necessary and is not covered** when criteria I., II., or III., are not met, including but not limited to the following:

A. Cancer risk assessment in the general population.
B. When the genetic variant reported in a family member is a variant of unknown significance (VUS) (also known as unclassified variant, variant of uncertain significance).
C. When testing in criteria II. above results in a positive test for the BRAF V600E mutation

and/or MLH1 promoter hypermethylation.

IV. Genetic panel testing which includes genes other than *APC, MUTYH, MLH1, MSH2, MSH6*, *PMS2* and/or *EPCAM* is considered **investigational and is not covered**, unless requested as part of a multi-gene panel that meets criteria per the Medical Policy, "Next Generation Sequencing for Cancer (All Lines of Business Except Medicare). Examples of investigational panels include, but are not limited to, the following:

A. Myriad myRisk® panel test
B. Ambry ColoNext® panel test
C. GeneDx Colorectal Cancer Panel test

Link to Evidence Summary

POLICY CROSS REFERENCES

- Genetic Counseling, MP316

The full Company portfolio of current Medical Policies is available online and can be accessed here.

POLICY GUIDELINES

Genetic Panel Testing

The clinical utility of testing has been established for all six of the genes listed above in the policy criteria. Therefore, when medical necessity criteria are met, genetic panel testing for Lynch and well-defined polyposis syndromes may include one or more of **any combination** of the genes listed in this section above. For example, genetic panels, such as the Myriad's COLARIS® panel test, which includes only the genes, or a subset of the genes, addressed in the medical necessity criteria (II.) above, may be considered medically necessary when criteria are met.

DOCUMENTATION REQUIREMENTS

In order to determine the clinical utility of a genetic test, the following documentation must be provided at the time of the request. Failure to submit complete documentation may affect the outcome of the review.

- Specific gene, trade or proprietary name of the test, or if a custom built test, include every gene(s) and/or component of the test
- Name of laboratory where the testing is being conducted or was conducted
- Clinical notes to include the following:
  - Documentation of genetic counseling as required in the Genetic Counseling policy which includes how test results will impact clinical decision making
  - If relevant, pre-test counseling notes should document the reason why an affected family member cannot be tested prior to testing an unaffected member

- Reason (indication) for performing test, including the suspected condition
- Existing signs and/or symptoms related to reason for current test request
- Prior test/laboratory results related to reason for current test request
- Family history, if applicable
- How results from current test request will impact clinical decision making

All relevant CPT/HCPCS codes billed

DEFINITIONS

*Close Blood Relatives

The National Comprehensive Cancer Network (NCCN) defines close blood relative as first- (parents, siblings and children), second- (grandparents, aunts, uncles, nieces and nephews, grandchildren and half-siblings), and third degree-relatives (great-grandparents, great-aunts, great uncles, great grandchildren and first cousins) on same side of family.

**Lynch Syndrome-Related Cancers

Lynch syndrome-related cancers include: colorectal, endometrial, gastric, ovarian, pancreatic, ureter or renal pelvis, brain (usually glioblastoma), small intestinal cancers, sebaceous adenomas and carcinomas, and keratoacanthomas as seen in Muir–Torre syndrome.

***MMR Gene Mutation Risk Prediction Models

- MMRpro: http://www4.utsouthwestern.edu/breasthealth/cagene/
- PREMM5: http://premm.dfci.harvard.edu/
- MMRpredict: http://hnpccpredict.hgu.mrc.ac.uk/

BACKGROUND
Clinical Utility of Genetic Testing

Establishing the clinical utility of any test is a key component in determining its ultimate usefulness. Clinical utility may be established when published evidence demonstrates test results can be used to:

1. Guide treatment, management, or preventive decisions; **and**
2. Those decisions lead to improved primary health outcomes.

Genetic Panel Testing

Numerous genetic panels are available which test for various combinations of genes associated with hereditary colorectal cancers. Some well-designed genetic panel tests include only the genes that have demonstrated clinical utility and high penetrance for Lynch and well-defined polyposis syndromes. However, other panel tests include a broader range of genes for these and other related cancer syndromes for which penetrance levels are intermediate and low and the clinical utility of testing is not yet established. It is not recommended that patients undergo testing for gene mutations with unknown clinical significance as test results may lead to unnecessary interventions and additional testing which is

not supported by current evidence or practice standards. Therefore, the clinical utility of each gene included in a panel must be demonstrated in order to establish the medical necessity of the panel test.

CLINICAL EVIDENCE AND LITERATURE REVIEW

CLINICAL PRACTICE GUIDELINES

The medical necessity criteria within this policy are primarily supported and guided by the National Comprehensive Cancer Network (NCCN) Genetic/Familial High-Risk Assessment: Colorectal clinical practice guidelines.

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines (v.1.2021) regarding genetic/familial high-risk assessment for colorectal cancer recommend a stepwise approach, with genetic testing performed in the following order:[1]

1. Individual with personal history of cancer and a known pathogenic variant in the family. In this case, a pathogenic variant includes likely pathogenic variants.
2. Individual with a personal history of polyps indicative of a polyposis syndrome.
3. Individual with a personal or family history of Lynch syndrome and LS-related cancers.

However, NCCN states that multi-gene testing has a number of advantages over sequential testing including that is more efficient, has a higher chance of providing an explanation for the cause of cancer, and the cost is similar to that of sequential testing.

In addition, NCCN states that there are many clinical scenarios in which multi-gene testing may be considered, with some examples including:

- When more than one gene can explain an inherited cancer syndrome (e.g., Lynch syndrome).
- When personal and/or family history meets criteria for more than one hereditary cancer syndrome (e.g., family meets both BRCA-related breast cancer and Lynch syndrome clinical criteria.
- When colonic polyposis has uncertain histology.

The NCCN guideline stated that multi-gene testing should be done in the context of pre- and post-test genetic counseling by certified genetic counselors or clinicians with extensive training in cancer genetics.

EVIDENCE SUMMARY

Medically Necessary Testing

There is enough research to show that genetic testing in genes *APC, MUTYH, MLH1, MSH2, MSH6, PMS2*, and/or *EPCAM* may improve overall health outcomes in people who might have Lynch and polyposis syndromes (FAP and MAP) and who have a family history of colorectal cancer. In addition, current clinical practice guidelines recommend genetic testing for individuals at high risk for these colorectal cancer syndromes. Therefore, genetic testing for Lynch and polyposis syndromes in genes *APC, MUTYH, MLH1, MSH2, MSH6, PMS2*, and/or *EPCAM* is considered medically necessary and covered when policy criteria are met.

There is enough research to show that genetic testing for a *BRAF* V600E mutation or for *MLH1* promoter methylation can help improve overall health outcomes for people a personal history of cancer. This type of testing may help exclude Lynch syndrome from the list of possible diagnoses. Testing could prevent the need for additional genetic testing and directs medical management. In addition, current clinical practice guidelines recommend testing for *BRAF* V600E or *MLH1* promoter methylation as part of the evaluation of patients with specific selection criteria. Therefore, *BRAF* V600E mutation or *MLH1* promoter methylation testing may be considered medically necessary and covered when policy criteria are met.

Not Medically Necessary Testing

Genetic testing for Lynch and polyposis syndromes has not been shown to lead to improved health outcomes for individuals who do not have specific risk factors, as outlined in the policy criteria above. Certain testing may lead overtreatment and over-screening (more tests). One example of this type of unnecessary testing includes testing for a known familial variant that has been reported as a variant of uncertain significance (VUS). Testing of this nature leads to uncertain clinical management. In addition, current clinical practice guidelines do not support testing in these situations. Therefore, genetic testing for Lynch and polyposis syndromes is considered not medically necessary and not covered when policy criteria are not met.

Investigational Testing

There is not enough research to show that multi-gene panel testing including genes other than *APC, MUTYH, MLH1, MSH2, MSH6, PMS2*, and/or *EPCAM* for Lynch and polyposis syndromes leads to improved health outcomes. In addition, current clinical practice guidelines do not support testing in these situations. Therefore, genetic testing for Lynch and polyposis syndromes using multi-gene panel testing including genes *other* than *APC, MUTYH, MLH1, MSH2, MSH6, PMS2*, and/or *EPCAM* is considered investigational and not covered.

BILLING GUIDELINES AND CODING

CODES*		
CPT	0101U	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated (15 genes [sequencing and deletion/duplication], EPCAM and GREM1 [deletion/duplication only])
	0130U	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), targeted mRNA sequence analysis panel (APC, CDH1, CHEK2, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, and TP53) (List separately in addition to code for primary procedure)

	0157U	APC (APC regulator of WNT signaling pathway) (eg, familial adenomatosis polyposis [FAP]) mRNA sequence analysis (List separately in addition to code for primary procedure)
	0158U	MLH1 (mutL homolog 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
	0159U	MSH2 (mutS homolog 2) (eg, hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
	0160U	MSH6 (mutS homolog 6) (eg, hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
	0161U	PMS2 (PMS1 homolog 2, mismatch repair system component) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
	0162U	Hereditary colon cancer (Lynch syndrome), targeted mRNA sequence analysis panel (MLH1, MSH2, MSH6, PMS2) (List separately in addition to code for primary procedure)
	0238U	Oncology (Lynch syndrome), genomic DNA sequence analysis of MLH1, MSH2, MSH6, PMS2, and EPCAM, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
	81201	APC (adenomatous polyposis coli)(e.g. familial adenomatosis polyposis[FAP] gene analysis, full gene sequence
	81202	APC (adenomatous polyposis coli)(e.g. familial adenomatosis polyposis [FAP] gene analysis, known familial variants
	81203	APC (adenomatous polyposis coli)(e.g. familial adenomatosis polyposis [FAP] gene analysis; duplication/deletion variants
	81210	BRAF (v-raf murine sarcoma viral oncogene homolog B1) (e.g. Colon Cancer) gene analysis, V600E variant
	81288	MLH1 (mutl. Homolog1, colon cancer, non-polyposis type 2 (e.g. hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
	81292	MLH1 (mutl. Homolog1, colon cancer, non-polyposis type 2 (e.g. hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81293	MLH1 (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, 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; known familial variants
	81299	MSH6 (mutS homolog 6 [E.coli])(e.g. hereditary nonpolyposis 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
	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 [S. cerevisiae]) (e.g., hereditary non- polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
	81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) – when used for MUTYH (mutY homolog [E. coli]) (eg, MYH-associated polyposis), common variants (eg, Y165C, G382D)
	81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons) – when used for EPCAM (epithelial cell adhesion molecule) (eg, Lynch syndrome), duplication/deletion analysis
	81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) – when used for MUTYH (mutY homolog [E. coli]) (eg, MYH-associated polyposis), full gene sequence
	81435	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11
	81436	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); duplication/deletion analysis panel, must include analysis of at least 5 genes, including MLH1, MSH2, EPCAM, SMAD4, and STK11
	81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis

	81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
	81479	Unlisted molecular pathology procedure
HCPCS	None	

***Coding Notes:**

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

REFERENCES

1. National Comprehensive Cancer Network. NCCN guidelines. Genetic/Familial High-Risk Assessment: Colorectal. Version 1.2021. May 11, 2021. https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf. Accessed 4/18/2022.

POLICY REVISION HISTORY

DATE	REVISION SUMMARY
2/2023	Converted to new policy template.