



MASSACHUSETTS

Blue Cross Blue Shield of Massachusetts is an Independent Licensee of the Blue Cross and Blue Shield Association

Medical Policy

Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Table of Contents

- [Policy: Commercial](#)
- [Coding Information](#)
- [Information Pertaining to All Policies](#)
- [Policy: Medicare](#)
- [Description](#)
- [References](#)
- [Authorization Information](#)
- [Policy History](#)

Policy Number: 226

BCBSA Reference Number: 2.04.08

NCD/LCD:

- Local Coverage Determination (LCD): MoIDX: Genetic Testing for Lynch Syndrome (L35024)
- Local Coverage Determination (LCD): MoIDX: APC and MUTYH Gene Testing (L36827)
- Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

Related Policies

KRAS, NRAS, and BRAF Variant Analysis in Metastatic Colorectal Cancer, #[104](#)

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

Genetic testing for APC gene mutations may be **MEDICALLY NECESSARY** in the following patients:

- At-risk relatives* of patients with FAP and/or a known APC mutation or
- Patients with a differential diagnosis of attenuated FAP vs. *MUTYH*-associated polyposis vs. Lynch syndrome. Whether testing begins with APC mutations or screening for MMR mutations depends upon clinical presentation.

* "At-risk relatives" are first-degree relatives. In cases of small family pedigree, extended family members may be included in testing.

Genetic testing for *MUTYH* gene mutations may be **MEDICALLY NECESSARY** in the following patients:

- Patients with a differential diagnosis of attenuated FAP vs. *MUTYH*-associated polyposis vs. Lynch syndrome and a negative result for APC gene mutations. Family history of no parents or children with FAP is consistent with *MUTYH*-associated polyposis (autosomal recessive).

Genetic testing for MMR gene mutations is may be **MEDICALLY NECESSARY** in the following patients:

- Patients with colorectal cancer, for the diagnosis of Lynch syndrome.
- Patients with endometrial cancer and one first-degree relative diagnosed with a Lynch-associated cancer for the diagnosis of Lynch syndrome
- At-risk relatives of patients with Lynch syndrome with a known MMR mutation.

- Patients with a differential diagnosis of attenuated FAP vs. *MUTYH*-associated polyposis vs. Lynch syndrome. Whether testing begins with APC mutations or screening for MMR mutations depends upon clinical presentation.
- Patients without colorectal cancer but with a family history meeting the Amsterdam or Revised Bethesda criteria, when no affected family members have been tested for MMR mutations.

Genetic testing for *EPCAM* mutations may be **MEDICALLY NECESSARY** when any one of the following 3 major bulleted criteria are met:

- Patients with colorectal cancer, for the diagnosis of Lynch syndrome when:
 - Tumor tissue shows lack of *MSH2* expression by immunohistochemistry and patient is negative for a germline mutation in *MSH2*; or
 - Tumor tissue shows a high level of microsatellite instability and patient is negative for a germline mutation in *MSH2*, *MLH1*, *PMS2*, and *MSH6*; OR
- At-risk relatives of patients with Lynch syndrome with a known *EPCAM* mutation; OR
- Patients without colorectal cancer but with a family history meeting the Amsterdam or Revised Bethesda criteria, when no affected family members have been tested for MMR mutations, and when sequencing for MMR mutations is negative.

Genetic testing for *BRAF* V600E or *MLH1* promoter methylation may be considered **MEDICALLY NECESSARY** to exclude a diagnosis of Lynch syndrome when *MLH1* protein is not expressed in a colorectal cancer on immunohistochemical (IHC) analysis.

Pre- and post-test genetic counseling may be **MEDICALLY NECESSARY** as an adjunct to the genetic testing itself.

Genetic testing for all other gene mutations for Lynch syndrome or colorectal cancer is **INVESTIGATIONAL**.

Following the Medical Policy Administration review process, Blue Cross Blue Shield of Massachusetts has determined that genetic testing for APC gene mutations for colorectal cancer patients with classical FAP is considered **NOT MEDICALLY NECESSARY**.

Amsterdam II Clinical Criteria

The Amsterdam criteria are the most stringent criteria for defining families at high risk for Lynch Syndrome:

- 3 or more relatives with an associated cancer (colorectal cancer, or cancer of the endometrium, small intestine, ureter or renal pelvis);
- 1 should be a first-degree relative of the other 2;
- 2 or more successive generations affected;
- 1 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 HNPCC with only 2 colorectal cancers in first-degree relatives if at least 2 generations have the cancer and at least one case of colorectal cancer was diagnosed by the age of 55 years;
 - OR: in families with 2 first-degree relatives affected by colorectal cancer, the presence of a third relative with an unusual early-onset neoplasm or endometrial cancer is sufficient.

Revised Bethesda Guidelines

The Bethesda guidelines are less strict than the Amsterdam criteria and are intended to increase the sensitivity of identifying at-risk families. The Bethesda guidelines are also felt to be 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 (at the same time) or metachronous (at another time i.e. - a recurrence of) CRC or other Lynch syndrome-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 with one or more first-degree relatives with an HNPCC-related tumor (colorectal, endometrial, stomach, ovarian, pancreas, bladder, ureter and renal pelvis, biliary tract, brain [usually glioblastoma as seen in Turcot syndrome], sebaceous bland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel), with one of the cancers being diagnosed at younger than age 50 years, OR CRC diagnosed in 2 or more first- or second-degree relatives with HNPCC-related tumor, regardless of age.

Medicare HMO BlueSM and Medicare PPO BlueSM Members

Medical necessity criteria and coding guidance for **Medicare Advantage members living in Massachusetts** can be found through the links below.

[Local Coverage Determination \(LCD\): MolDX: Genetic Testing for Lynch Syndrome \(L35024\)](#)

[Local Coverage Determination \(LCD\): MolDX: APC and MUTYH Gene Testing \(L36827\)](#)

[Local Coverage Determination \(LCD\): Molecular Pathology Procedures \(L35000\)](#)

For medical necessity criteria and coding guidance for **Medicare Advantage members living outside of Massachusetts**, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at <https://www.cms.gov>.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

| | Outpatient |
|---------------------------------------|--|
| Commercial Managed Care (HMO and POS) | Prior authorization is not required . |
| Commercial PPO and Indemnity | Prior authorization is not required . |
| Medicare HMO Blue SM | Prior authorization is not required . |
| Medicare PPO Blue SM | Prior authorization is not required . |

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above **medical necessity criteria MUST** be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue

CPT Codes

| CPT codes: | Code Description |
|------------|--|
| 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-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600E 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 gene analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome); full sequence analysis |
| 81293 | MLH1 gene analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome); known familial variants |
| 81294 | MLH1 gene analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome); duplication/deletion variants |
| 81295 | MSH2 (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis |
| 81296 | MSH2 (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants |
| 81297 | MSH2 (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants |
| 81298 | MSH6 (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis |
| 81299 | MSH6 (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants |
| 81300 | MSH6 (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants |
| 81301 | Microsatellite instability analysis (eg, , hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed |
| 81317 | PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis |
| 81318 | PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants |
| 81319 | PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants |

The following CPT codes are considered investigational for **Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:**

CPT Codes

| CPT codes: | Code Description |
|------------|--|
| 81435 | Hereditary colon cancer syndromes (eg, Lynch syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, must include analysis of at least 7 genes, including APC, CHEK2, MLH1, MSH2, MSH6, MUTYH, and PMS2 |

| | |
|-------|---|
| 81436 | Hereditary colon cancer syndromes (eg, Lynch syndrome, familial adenomatous polyposis); duplication/deletion gene analysis panel, must include analysis of at least 8 genes, including APC, MLH1, MSH2, MSH6, PMS2, EPCAM, CHEK2, and MUTYH |
|-------|---|

Description

Genetic testing is available for both affected individuals, as well as those at risk, for various types of hereditary colon cancer, including familial adenomatous polyposis (FAP), Lynch Syndrome (formerly known as HNPCC), and *MUTYH*-associated polyposis.

There are currently 2 well-defined types of hereditary colorectal cancer, FAP and Lynch syndrome. FAP can be identified by the appearance of hundreds to thousands of characteristic, precancerous colon polyps. If left untreated, all affected individuals will go on to develop colorectal cancer. Germline mutations in the adenomatous polyposis coli gene are responsible for FAP and are inherited in an autosomal dominant manner. Patients with Lynch syndrome have a predisposition to colorectal cancer and other malignancies as a result of an inherited mutation in a DNA mismatch repair (MMR) gene. Lynch syndrome includes those with an existing cancer and those who have not yet developed cancer.

MUTYH-associated polyposis (MAP) is a hereditary condition that is caused by mutations in the *MUTYH* gene. Patients with MAP may have hundreds of polyps in their colon and rectum, and are at an increased risk for developing colorectal cancer.

Various attempts have been made to identify which patients with colon cancer should undergo testing for MMR mutations, based primarily on family history and related characteristics. The Evaluation of Genomic Applications in Practice and Prevention Working Group recommended testing all patients with colorectal cancer for Lynch syndrome. This recommendation includes genetic testing for the following types of patients:

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

Summary

Results of testing for the adenomatous polyposis coli (*APC*) mutation in individuals with a family history of familial adenomatous polyposis (FAP), or a known *APC* mutation in the family, lead to changes in surveillance and prophylactic treatment. For patients with a positive result, enhanced surveillance and/or prophylactic treatment will reduce the future incidence of colon cancer and improve health outcomes. Therefore, *APC* testing is medically necessary for patients with a family history of FAP or a known *APC* mutation in the family. A related familial polyposis syndrome, *MUTYH*-associated polyposis (MAP) syndrome, is associated with mutations in the *MUTYH* gene. Testing for this genetic mutation is medically necessary when the differential diagnosis includes both FAP and MAP, since distinguishing between the two leads to different management strategies. In some cases, Lynch syndrome may be part of the same differential diagnosis, depending on presentation.

A substantial portion of patients with colorectal cancer will be found to have Lynch syndrome, which is associated with mutations in the mismatch repair (*MMR*) gene. A positive genetic test for the *MMR* mutation can lead to enhanced surveillance, changes in recommendations about treatment options, and possible prophylactic treatment for other Lynch syndrome malignancies. Therefore, testing for Lynch syndrome in patients with newly diagnosed colorectal cancer and in patients at high risk for Lynch syndrome, defined by meeting the clinical criteria such as Amsterdam II or Revised Bethesda, is considered medically necessary. Additionally, immunohistochemical (IHC) testing for *BRAF V600E* or

MLH1 promoter methylation may be considered medically necessary to exclude a diagnosis of Lynch syndrome when *MLH1* is not expressed in the colorectal tumor.

Women with endometrial cancer are also at risk for Lynch syndrome, at a low prevalence; the prevalence is increased substantially when the population is limited to those (at any age) with a first-degree relative diagnosed with a Lynch-associated cancer. Those found to have a *MMR* mutation will also benefit from enhanced colorectal cancer surveillance and prophylactic treatments. Therefore, testing for Lynch syndrome in patients with newly diagnosed endometrial cancer who also have a first-degree relative diagnosed with a Lynch-associated cancer may be considered medically necessary. The *EPCAM* mutation is less common than *MMR* mutations as a cause of Lynch syndrome and should be part of the diagnostic testing for Lynch syndrome in patients who are negative for all *MMR* mutations but who screen positive for microsatellite instability (MSI) and lack *MSH2* immunohistochemistry evidence of protein expression.

Policy History

| Date | Action |
|----------------|---|
| 9/2018 | Local Coverage Determination (LCD) Molecular Pathology Procedures (L35000) added. 9/2018 |
| 10/2017 | New references added from BCBSA National medical policy. |
| 3/2016 | New references added from BCBSA National medical policy. |
| 1/2016 | Clarified coding information. |
| 7/2015 | Local Coverage Determination (LCD): MoIDX: Genetic Testing for Lynch Syndrome (L33779) added. |
| 6/2015 | Local Coverage Determination (LCD): Molecular Pathology Procedures (L34506) added. |
| 1/2015 | Clarified coding information. |
| 12/2014 | New references added from BCBSA National medical policy. |
| 4/2014 | BCBSA National medical policy review. New medically necessary and investigational indications described. Effective 4/1/2014. Coding information clarified. |
| 1/2014 | Updated to add new CPT code 88343. |
| 10/2013 | BCBSA National medical policy review. Title changed. |
| 6/2013 | BCBSA National medical policy review. New medically necessary indications described. Effective 6/1/2013. |
| 1/2013 | Updated to add new CPT codes 81201-81203 and 81317-81319 |
| 11/2011-4/2012 | Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements. |
| 10/2011 | Reviewed - Medical Policy Group – GI, Nutrition and Organ Transplantation. No changes to policy statements. |
| 7/2011 | Reviewed - Medical Policy Group – Hematology and Oncology. No changes to policy statements. |
| 11/2010 | Reviewed - Medical Policy Group – Gastroenterology, Nutrition and Organ Transplantation. No changes to policy statements. |
| 9/1/2010 | Medical Policy #226 effective 9/1/2010 created. |

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

[Medical Policy Terms of Use](#)

[Managed Care Guidelines](#)

[Indemnity/PPO Guidelines](#)

[Clinical Exception Process](#)

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