Lynch Syndrome AHS-M2004

Description of Procedure or Service

Lynch syndrome (LS) (also known as hereditary non-polyposis colorectal cancer; HNPCC) is the most common form of hereditary colorectal (CRC) and endometrial cancers (EMC), resulting from an autosomal dominant inactivation of any of four mismatch repair (MMR) genes (MLH1, MSH2, MSH6, and PMS2) leading to microsatellite instability (MSI) (Rumilla et al., 2011) and associated with an increased risk of colorectal, endometrial, stomach, small bowel, and ovarian cancers (Hunter et al., 2015; Lynch et al., 2009; Moreira et al., 2012).

Related Policies:
- Familial Adenomatous Polyposis and MUTYH-Associated Polyposis AHS-M2024
- Genetic Cancer Susceptibility Using Next Generation Sequencing AHS-M2066
- Molecular Panel Testing of Cancers to Identify Targeted Therapy AHS-M2109

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for Lynch Syndrome when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Lynch Syndrome is covered

Lynch syndrome is considered medically necessary for the following:

A. Genetic counseling is considered medically necessary for individuals undergoing Lynch Syndrome (LS) testing. Genetics counseling is required prior to undergoing testing for LS testing.

B. Testing for a known deleterious LS mutation is considered medically necessary for individuals when a familial mutation is identified in a tissue specimen of an affected family member. Risk assessment should be limited to testing for the known familial mutation and not for other mutations.
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C. If no known LS mutation AND colorectal or endometrial tumor tissue is available, then tumor testing with immunohistochemistry (IHC) and/or microsatellite instability (MSI) is considered medically necessary (Note 1).

D. If no known LS mutation AND sufficient colorectal or endometrial tumor tissue is NOT available, then LS-specific testing - MLH1, MSH2, MSH6, PMS2, and EPCAM OR multigene testing that includes concurrent testing of MLH1, MSH2, MSH6, PMS2, and EPCAM is considered medically necessary for an individual meeting criteria in Note 1. For expanded panel testing, please refer to policy AHS-M2109 Molecular Panel Testing of Cancers to Identify Targeted Therapy.

E. When Predictive testing is offered to an individual, the following limitations apply:

a. Testing of the tumor of the affected family member should occur first, if possible, to identify a familial mutation.

b. When a familial mutation is identified in a tissue specimen of an affected family member, other family members being offered predictive testing for risk assessment should be limited to testing for the known familial mutation, and not for other mutations.

c. Individuals, in whom deleterious mutations are found, should be counseled on their risk of developing cancer or having a recurrence of cancer, and offered a plan for increased surveillance and intervention, if warranted.

d. Genetic testing for Lynch Syndrome is limited to once per lifetime, unless testing for additional clinically relevant mutations is warranted.

When Lynch Syndrome is not covered

Genetic testing for susceptibility to colorectal cancer is considered **investigational** for all other purposes, including, but not limited to, testing of the general population.

LS-specific testing or multi-gene testing as a universal testing strategy without IHC or MSI, is considered **investigational** for individuals, if no known familial LS mutation and colorectal (or endometrial) tumor tissue is available.

Note 1: According to the NCCN, “tumor screening for MMR deficiency is appropriate for all colorectal and endometrial cancers regardless of age at diagnosis, however, germline genetic testing is generally reserved for patients with early age at diagnosis; positive family history; or abnormal tumor testing results: MSI or loss of MMR protein expression (NCCN, 2018, 2019).”

Note 2: According to the criteria for the evaluation of Lynch Syndrome according to the NCCN guidelines version 3.2019, an individual must meet at least one of the following (NCCN, 2018, 2019):

1. An individual with colorectal or endometrial cancer and any of the following:
   a. Diagnosed before the age of 50 years
   b. Another synchronous or metachronous LS-related cancer (See Note 3)
   c. At least one first-degree or second-degree relative with LS-related cancer diagnosed by the age of 50 years (See Note 3)
   d. At least two first-degree or second-degree relatives with LS-related cancers regardless of age (See Note 3)

2. An individual with colorectal, endometrial, or other LS-related cancer (See Note 3) at any age with tumor showing evidence of mismatch repair (MMR) deficiency, either by microsatellite instability (MSI) or loss of MMR protein expression.

3. Family history of any of the following:
   a. At least one first-degree relative with colorectal or endometrial cancer diagnosed by the age of 50 years
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b. At least one first-degree relative with colorectal or endometrial cancer AND another synchronous or metachronous LS-related cancer (See Note 3)
c. At least two first-degree or second-degree relatives with LS-related cancer (See Note 3) AND at least one of the relatives must be diagnosed by the age of 50 years
d. At least three first-degree or second-degree relatives with LS-related cancers (See Note 3), regardless of age

4. An individual with a LS-related cancer (See Note 3) or unaffected individual with at least a 5% risk of having an MMR gene pathogenic variant based on predictive models (PREMM5, MMRpro, MMRpredict)

5. An individual with a colorectal tumor with MSI-high (MSI-H) histology—i.e. presence of tumor-infiltrating lymphocytes, Crohn’s-like lymphocytic reaction, mucinous/signet ring differentiation, or medullary growth pattern.

Note 3: According to the NCCN, “LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, brain (usually glioblastoma), biliary tract, small intestinal cancers, as well as sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas as seen in Muir-Torre syndrome (NCCN, 2018, 2019).”

Policy Guidelines

Lynch syndrome (LS) is recognized by a hereditary predisposition to colorectal, endometrial, and other cancers due to inactivation by germline mutations or epigenetic silencing in any of the four DNA mismatch repair genes—MLH1, MSH2, MSH6, and PMS2. Mutations in MLH1 and MSH2 are most common (90%) followed by MSH6 (10%) and PMS2 (6%) (Jansen, Menko, Brosens, Giardiello, & Offerhaus, 2014). Mutations of the upstream EPCAM gene which result in silencing of the MSH2 gene produce a phenotype very similar to LS (Ligtenberg et al., 2009). LS accounts for approximately 1% to 3% of all colorectal cancers and 2% to 5% of endometrial cancers (Hampel et al., 2005). In addition to colorectal and endometrial cancers, patients may present with ovarian, urinary tract, stomach, small bowel, hepatobiliary, sebaceous gland and central nervous system neoplasms (Barrow, Khan, Laloo, Evans, & Hill, 2013).

The lifetime risk of CRC is greatly increased in LS patients, but varies significantly from 10-74% dependent on which MMR gene is inactivated (Brosens, Offerhaus, & F, 2015). Average age at CRC diagnosis in LS patients is 44 to 61 years with tumors primarily arising proximal to the splenic flexure (Giardiello et al., 2014b). There is also a high rate of metachronous CRC (16% at 10 years; 41% at 20 years) in LS patients (Win et al., 2013). The histopathology of LS colorectal cancer is often poorly differentiated, with signet cell histology, abundant extracellular mucin, tumor infiltrating lymphocytes, and a lymphoid host response to tumor (Peltonäki PT, 2010). LS patients have improved survival rates compared to similar stage spontaneous CRC (Brosens et al., 2015). Life time risk of endometrial cancer is significantly increased to 15 – 71% of women with mutation specific variability (Giardiello et al., 2014b). Increased life time risks has also been observed in urinary, ovarian, stomach, hepatobiliary, small bowel, brain, pancreatic and prostate cancers (Brosens et al., 2015).

Cancer Risks in Individuals with Lynch Syndrome Age ≤70 Years Compared to the General Population (Brosens et al., 2015)

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>General Population Risk</th>
<th>Lynch Syndrome (MLH1 and MSH2 heterozygotes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk</td>
<td>Risk</td>
</tr>
<tr>
<td>Colon</td>
<td>4.8%</td>
<td>52%-82%</td>
</tr>
<tr>
<td>Endometrium</td>
<td>2.7%</td>
<td>25%-60%</td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt;1%</td>
<td>6%-13%</td>
</tr>
<tr>
<td>Ovary</td>
<td>1.4%</td>
<td>4%-12%</td>
</tr>
</tbody>
</table>
Several sets of clinical criteria have been developed to identify patients with LS. In 1990, the International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer (HNPCC) established criteria (Amsterdam I Criteria) for HNPCC (Vasen, Mecklin, Khan, & Lynch, 1991), which were updated to be more sensitive in 1999 (Vasen, Watson, Mecklin, & Lynch, 1999). The Revised Bethesda Guidelines are a third set of clinicopathologic criteria developed in 2004 to improve identification of individuals who deserve investigation for LS; however, they state, “The goal of the Bethesda Guidelines is to identify HNPCC patients, not to identify MSI-H tumors from patients in sporadic populations that may have better prognoses or different therapeutic implications (Umar et al., 2004).”

**Clinical Utility and Validity**

Statistical models to predict risk of MMR mutations include PREMM5, MMRpredict, and MMRpro. The PREMM5 clinical prediction algorithm, available at [http://premm.dfci.harvard.edu/](http://premm.dfci.harvard.edu/), “estimates the cumulative probability of an individual carrying a germline mutation in the MLH1, MSH2, MSH6, PMS2, or EPCAM genes” using an individual’s personal and family history of colorectal cancer, endometrial cancer, or other LS-related cancers with the results given as a percentage of overall predicted probability of mutation in one of the four LS-related genes (DFCI, 2016). A study using the clinical and germline data from more than 18,000 individuals published in 2017 validated the use of the PREMM5 model. The report shows that for the four LS-related genes PREMM5 can distinguish “carriers from noncarriers with an AUC of 0.81 (95% CI, 0.79 to 0.82), and performance was similar in the validation cohort (AUC, 0.83; 95% CI, 0.75 to 0.92). Prediction was more difficult for PMS2 mutations (AUC, 0.64; 95% CI, 0.60 to 0.68) than for other genes.” The authors conclude, “PREMM5 provides comprehensive risk estimation of all five LS genes and supports LS genetic testing for individuals with scores ≥ 2.5% (Kastrinos et al., 2017).”

MMRpro, statistical model and software using family history of colorectal and endometrial cancers, is available for free download at [http://www4.utsouthwestern.edu/breasthealth/cagene/](http://www4.utsouthwestern.edu/breasthealth/cagene/). “The results give useful information about an individual's colon cancer risk before he or she decides to undergo invasive screenings or expensive genetic testing (Harvard, 2019).” A study released in 2015 concluded that MMRpro was comparable to the PREMM1,2,6 model in discriminating both clinic- and population-based cohorts (Kastrinos et al., 2016). Another study in 2017 investigated the use of MMRpro in predicting MLH1 mutations since, unlike the other LS-related genes, immunohistochemistry is less sensitive as a prescreening test for these mutations. By limiting the scope of the study to MLH1 mutations, MMRpro outperforms the PREM1,2,6 algorithm (AUC 0.83 versus 0.68, respectively). The authors state, “Considering a threshold of 5 %, MMRpro would eliminate unnecessary germline mutation analysis in a significant proportion of cases while keeping very high sensitivity. We conclude that MMRpro is useful to correctly predict who should be screened for a germline MLH1 gene mutation and propose an algorithm to improve the cost-effectiveness of LS diagnosis (Cabreira et al., 2017).”

Likewise, the MMRpredict algorithm, available at [http://hnpppredict.hgu.mrc.ac.uk/](http://hnpppredict.hgu.mrc.ac.uk/), is jointly operated by the Colon Cancer Genetics Group at the University of Edinburgh and MRC Human Genetics Unit of Edinburgh. This algorithm predicts the probability of a mutation carrier of an affected individual using criteria consisting of the age at time of diagnosis, gender, tumor location, synchronicity of tumor, and

<table>
<thead>
<tr>
<th>Region</th>
<th>Risk</th>
<th>Age</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatobiliary tract</td>
<td>&lt;1%</td>
<td>1.4%-4%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>&lt;1%</td>
<td>1%-4%</td>
<td>~55 years</td>
</tr>
<tr>
<td>Small bowel</td>
<td>&lt;1%</td>
<td>3%-6%</td>
<td>49 years</td>
</tr>
<tr>
<td>Brain.central nervous system</td>
<td>&lt;1%</td>
<td>1%-3%</td>
<td>~50 years</td>
</tr>
<tr>
<td>Sebaceous neoplasms</td>
<td>&lt;1%</td>
<td>1%-9%</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
family history (MRC, 2014). A 2018 study shows that MMRpredict performs better than the PREMM5 model in identifying PMS2 mutation carriers (AUCs 0.72 and 0.51, respectively), and the efficacy of the PREMM5 model is more dependent on the location of the tumor. Both algorithms were comparable in predicting MLH1 and MSH2 mutation carriers (Goverde et al., 2018). These data apparently contradict earlier findings where a previous version of the PREMM model, PREM1,2,6, performed better than MMRpredict in predicting carriers of MLH1, MSH2, or MSH6 gene mutations. “For clinic- and population-based cohorts, O/E [observed-to-expected ratio] deviated from 1 for MMRpredict (0.38 and 0.31, respectively) and MMRPro (0.62 and 0.36) but were more satisfactory for PREMM1,2,6 (1.0 and 0.70). MMRPro or PREMM1,2,6 predictions were clinically useful at thresholds of 5% or greater and in particular at greater than 15% (Kastrinos et al., 2016).”

However, as use of clinical criteria and modeling to identify patients with LS has less than optimal sensitivity and can vary in efficacy between different ethnic populations (Lee et al., 2016), universal screening for LS (Cohen et al., 2016; Kidambi et al., 2015) has been recommended (Proenzalle et al., 2016). Analysis by immunohistochemical testing for the MLH1/MSH2/MSH6/PMS2 proteins and/or MSI testing are commonly used to screen for LS phenotypes (Syngal et al., 2015). Tumors with loss of MLH1 should undergo analysis to exclude BRAF mutation or MLH1 promoter hypermethylation according to the USPSTF (Giardiello et al., 2014). Moreover, patients with evidence of LS should be referred for genetic evaluation (EGAPP, 2009; Robson et al., 2015; Sepulveda et al., 2017).

Applicable Federal Regulations:
On October 27, 2017 the FDA approved VENTANA MMR IHC Panel for patients diagnosed with colorectal cancer (CRC) to detect mismatch repair (MMR) proteins deficiency as an aid in the identification of probable Lynch syndrome and to detect BRAFV600E protein as an aid to differentiate between sporadic CRC and probable Lynch syndrome.

Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA ’88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Guidelines and Recommendations

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group

In 2009, the EGAPP Working Group recommended (EGAPP, 2009):

1. Offering genetic testing for Lynch Syndrome to individuals with newly diagnosed colorectal cancer (CRC) to reduce morbidity and mortality in relatives. However, they do not recommend a specific testing protocol.

2. That individuals with newly diagnosed CRC should be routinely offered counseling and educational materials aimed at informing them and their relatives of the potential benefits and harms associated with genetic testing to identify Lynch Syndrome.

3. Microsatellite instability (MSI) testing or immunohistochemical (IHC) testing (with or without BRAF mutation testing) of the tumor tissue are examples of preliminary testing strategies that could be used to select patients for subsequent diagnostic testing. Diagnostic testing involves MMR gene mutation (and deletion/duplication) testing of the proband, usually using a blood sample. Lynch syndrome is most commonly caused by mutations in the two MMR genes MLH1 and MSH2; less commonly by mutations in MSH6 and PMS2.”

National Comprehensive Cancer Network (NCCN)

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The NCCN lists the following criteria for the evaluation of Lynch Syndrome:

- “Known LS mutation in the family
- An individual with colorectal or endometrial cancer and any of the following:
  - Diagnosed <50y
  - Another synchronous or metachronous LS-related cancer
  - ≥1 first-degree or second-degree relative with LS-related cancer diagnosed <50y
  - ≥2 first-degree or second-degree relatives with LS-related cancers regardless of age
- An individual with colorectal or endometrial cancer at any age with tumor showing evidence of mismatch repair (MMR) deficiency, either by microsatellite instability (MSI) or loss of MMR protein expression
- Family history of any of the following:
  - ≥1 first-degree relative with colorectal or endometrial cancer diagnosed <50y
  - ≥1 first-degree relative with colorectal or endometrial cancer and another synchronous or metachronous LS-related cancer
  - ≥2 first-degree or second-degree relatives with LS-related cancer, including ≥1 diagnosed <50y
  - ≥3 first-degree or second-degree relatives with LS-related cancers, regardless of age
- An individual with a LS-related cancer or unaffected individual with a ≥5% risk of having an MMR gene mutation based on predictive modes (PREMM5, MMRpro, MMRPredict)
- An individual with colorectal tumor with MSI-high (MSI-H) histology (ie, presence of tumor-infiltrating lymphocytes, Crohn’s-like lymphocytic reaction, mucinous/signet ring differentiation, or medullary growth pattern) diagnosed ≤60 y”.

The NCCN considers LS-related cancers to “include colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, brain (usually glioblastoma), biliary tract, small intestinal cancers, as well as sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas as seen in Muir-Torre syndrome.”

The NCCN also specifically states the following: “Tumor screening for MMR deficiency is appropriate for all colorectal and endometrial cancers regardless of age at diagnosis, however, germline genetic testing is generally reserved for patients with early age at diagnosis; positive family history; or abnormal tumor testing results: MSI or loss of MMR protein expression (NCCN, 2019).”

The 2019 version 1 guidelines do not recommend multi-gene testing under the following circumstances:
1) “there is an individual from a family with a known mutation and there is no other reason for multi-gene testing;
2) the patient’s family history is strongly suggestive of a known hereditary syndrome; and,
3) the patient is diagnosed with CRC with MSI or loss of one or more DNA MMR proteins (NCCN, 2019).”

Multigene testing may be considered in the following scenarios:
- “A patient with a personal or family history that meets criteria for >1 hereditary cancer syndrome (eg, Lynch syndrome and BRCA-related breast and/or ovarian cancer)
- Colonic polyposis with uncertain histology
- Adenomatous polyposis (specific to APC, MUTYH, POLE, and POLD1)
- Family history does not meet criteria for established testing guidelines but there is suspicion of hereditary cancer, and an appropriate panel is available
- Family history is limited or unknown, but patient has concerns about hereditary cancer
- As second-line testing when first-line testing is inconclusive (NCCN, 2019)”

National Institute for Health and Care Excellence (NICE)

NICE, in 2017, released their guidelines concerning molecular testing for LS in people with CRC.
The recommend the following (NICE, 2017):

- “Offer testing to all people with colorectal cancer, when first diagnosed, using immunohistochemistry for mismatch repair proteins or microsatellite instability testing to identify tumours with deficient DNA mismatch repair, and to guide further sequential testing for Lynch syndrome... Do not wait for the results before starting treatment.
- “If using immunohistochemistry, follow the steps in table 1.”

### Table 1: Steps in the immunohistochemistry testing strategy (NICE, 2017)

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>Do an immunohistochemistry 4-panel test for MLH1, MSH2, MSH6 and PMS2.</td>
</tr>
<tr>
<td>Step 2</td>
<td>If the MLH1 immunohistochemistry result is abnormal, use sequential BRAF V600E and MLH1 promoter hypermethylation testing to differentiate sporadic and Lynch syndrome-associated colorectal cancers. First do a BRAF V600E test.</td>
</tr>
<tr>
<td>Step 3</td>
<td>If the BRAF V600E test is negative, do an MLH1 promoter hypermethylation test.</td>
</tr>
<tr>
<td>Step 4</td>
<td>If the MLH1 promoter hypermethylation test is negative, confirm Lynch syndrome by genetic testing of germline DNA.</td>
</tr>
</tbody>
</table>

- “If using microsatellite instability testing, follow the steps in table 2.”

### Table 2: Steps in the microsatellite instability testing strategy (NICE, 2017)

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>Do a microsatellite instability test.</td>
</tr>
<tr>
<td>Step 2</td>
<td>If the microsatellite instability test result is positive, use sequential BRAF V600E and MLH1 promoter hypermethylation testing to differentiate sporadic and Lynch syndrome-associated colorectal cancers. First do a BRAF V600E test.</td>
</tr>
<tr>
<td>Step 3</td>
<td>If the BRAF V600E test is negative, do an MLH1 promoter hypermethylation test.</td>
</tr>
<tr>
<td>Step 4</td>
<td>If the MLH1 promoter hypermethylation test is negative, confirm Lynch syndrome by genetic testing of germline DNA.</td>
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</tbody>
</table>

- “Healthcare professionals should ensure that people are informed of the possible implications of test results for both themselves and their relatives, and ensure that relevant support and information is available. Discussion of genetic testing should be done by a healthcare professional with appropriate training (NICE, 2017).”

**American Society of Clinical Oncology (ASCO)**

The American Society of Clinical Oncology (ASCO) recommends that “genetic testing only be conducted in the setting of pre- and post-test counseling” (Robson, Storm, Weitzel, Wollins, & Offit, 2010). In 2015, ASCO stated that “identifying inherited mutations in genes such as *BRCA1*, *BRCA2*, and the genes associated with Lynch syndrome allows for interventions that can significantly reduce the development of cancer and improve survival. Targeted capture assays employing NGS technology allow for testing many genes simultaneously, including genes that would not necessarily have been tested using the phenotype-directed approach, as well as genes of less clearly established clinical utility” (Robson et al., 2015). According to ASCO, multi-gene panel testing is particularly useful in situations where there are multiple high-penetrance genes associated with a specific cancer, and “one example of such a situation is Lynch syndrome, when the results of immunohistochemical analysis are not available to direct testing” (Robson et al., 2015).

**U.S. Multi-Society Task Force on Colorectal Cancer**

In 2014, The U.S. Multi-Society Task Force on Colorectal Cancer (Giardiello et al., 2014; Rex et al., 2017):

- “Testing for MMR deficiency of newly diagnosed CRC should be performed. This can be done for
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all CRCs, or CRC diagnosed at age 70 years or younger, and in individuals older than 70 years who have a family history concerning for LS. Analysis can be done by IHC testing for the MLH1/MSH2/MSH6/PMS2 proteins and/or testing for MSI. Tumors that demonstrate loss of MLH1 should undergo BRAF testing or analysis of MLH1 promoter hypermethylation.” Also, “Individuals who have a personal history of a tumor showing evidence of MMR deficiency (without evidence of MLH1 promoter methylation); uterine cancer diagnosed at younger than age 50 years; a known family MMR gene mutation; fulfill Amsterdam criteria or revised Bethesda guidelines; and/or have a personal risk of ≥5% chance of LS based on prediction models should undergo genetic evaluation for LS.”

ASCP, CAP, AMP, and ASCO

American Society for Clinical Pathology (ASCP), College of American Pathologists (CAP), Association for Molecular Pathology (AMP), and American Society of Clinical Oncology (ASCO) issued guidelines in 2017 stating “BRAF p.V600 mutational analysis should be performed in deficient MMR tumors with loss of MLH1 to evaluate for Lynch Syndrome risk. Presence of a BRAF mutation strongly favors a sporadic pathogenesis. The absence of BRAF mutation does not exclude risk of Lynch syndrome”. In addition, they have added the following recommendation for clinicians: “clinicians should order mismatch repair status testing in patients with colorectal cancers for the identification of patients at high risk for Lynch syndrome and/or prognostic stratification” (Sepulveda et al., 2017).

American College of Gastroenterology (ACG)

In 2015, ACG issued the following practice guidelines for the management of patients with hereditary gastrointestinal cancer syndromes (Syngal et al., 2015):

- “All newly diagnosed colorectal cancers should be evaluated for mismatch repair deficiency.
- Analysis may be done by immunohistochemical (IHC) testing for the MLH1/MSH2/MSH6/PMS2 proteins and/or testing for microsatellite instability; 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 mismatch repair deficiency (and no demonstrated BRAF mutation or hypermethylation of MLH1), a known family mutation associated with LS, or a risk of ≥5% chance of LS based on risk prediction models should undergo genetic evaluation for LS.
- Genetic testing of patients with suspected LS should include germline mutation genetic testing for the MLH1, MSH2, MSH6, PMS2, and/or EPCAM genes or the altered gene(s) indicated by IHC testing.”

American Society of Colon and Rectal Surgeons

The American Society of Colon and Rectal Surgeons (Herzig et al., 2017) published guidelines which recommend (based on 2014 U.S. Multi-Society Task Force on Colorectal Cancer):

“Universal testing (tumor testing)
- Testing for MMR deficiency of newly diagnosed CRC should be performed
- This can be done for all CRCs or CRC diagnosed at age ≤70 y and in individuals >70 y who have a family history concerning for LS
- Analysis can be done by IHC testing for the MLH1/MSH2/MSH6/PMS2 proteins and/or testing for MSI
- Tumors that demonstrate loss of MLH1 should undergo BRAF testing or analysis of MLH1 promoter hypermethylation
- To facilitate surgical planning, tumor testing on suspected CRC should be performed on preoperative biopsy specimens, if possible
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Traditional testing (germline testing)

- Individuals who have a personal history of a Lynch syndrome–related tumor showing evidence of MMR deficiency (without evidence of MLH1 promoter methylation)
- Personal history of uterine cancer diagnosed at age <50 y
- A known family MMR gene mutation
- Fulfill Amsterdam criteria or revised Bethesda guidelines
- Have a personal risk of ≥5% chance of LS based on prediction models

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina website at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81288, 81292, 81293, 81294, 81295, 81296, 81297, 81298, 81299, 81300, 81301, 81317, 81318, 81319, 81403, 88341, 88342, 88344, 96040, S0265

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


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Medical Director review 5/2019

Specialty Matched Consultant Advisory Panel 8/2019

Medical Director review 4/2020

**Policy Implementation/Update Information**

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/1/2019</td>
<td>New policy developed. BCBSNC will provide coverage for Lynch syndrome when it is determined to be medically necessary and criteria are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)</td>
</tr>
<tr>
<td>5/14/19</td>
<td>Reviewed by Avalon 1st Quarter 2019 CAB. Added related policies to Description section. Extensively revised When Covered section. Added Note 1 to Not Covered section. Extensively revised Policy Guidelines section. Coding table revised. Medical Director review 5/2019. (lpr)</td>
</tr>
<tr>
<td>10/1/19</td>
<td>Specialty Matched Consultant Advisory Panel review 8/21/2019. No change to policy statement. Deleted coding table from Billing/Coding section. (lpr)</td>
</tr>
<tr>
<td>5/12/20</td>
<td>Reviewed by Avalon 1st Quarter 2020 CAB. Medical Director review 4/2020. Updated Notes 1-3 and references. (lpr)</td>
</tr>
</tbody>
</table>

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment
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and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.