Clinical Policy Title: Genetic testing for hereditary cancer susceptibility

Clinical Policy Number: 02.01.19

Effective Date: July 1, 2016
Initial Review Date: May 18, 2016
Most Recent Review Date: April 10, 2018
Next Review Date: April 2019

Policy contains:
- Genetic testing.
- Lynch syndrome.
- Mutation.

Related policies:
- CP# 02.01.02 Genetic testing for breast and ovarian cancer
- CP# 02.01.22 Breast cancer index genetic testing
- CP# 02.01.14 Gene expression profile testing for breast cancer
- CP# 02.01.08 Familial polyposis gene testing
- CP# 02.01.09 Genetic testing for rare diseases
- CP# 02.01.10 COLARIS® testing for Lynch syndrome

ABOUT THIS POLICY: Select Health of South Carolina has developed clinical policies to assist with making coverage determinations. Select Health of South Carolina's clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Select Health of South Carolina when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state and federal laws and regulatory requirements, the plan benefits and/or state and federal laws and regulatory requirements shall control. Select Health of South Carolina’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Select Health of South Carolina’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Select Health of South Carolina will update its clinical policies as necessary. Select Health of South Carolina’s clinical policies are not guarantees of payment.

Coverage policy

Select Health of South Carolina considers the use of genetic testing for hereditary cancer susceptibility to be clinically proven and, therefore, medically necessary when the following criteria are met (Romero 2018, Willis 2016, Riley 2010, Royal Australian College of General Practitioners 2012, National Comprehensive Cancer Network [NCCN] 2016, Rubenstein 2015, NCCN 2015, Hilgart 2012, Robson 2010, Quillin 2010):

- An individual has a personal or family history suggestive of an inherited cancer syndrome.
- The genetic test can be adequately interpreted.
- Testing will influence medical management of the patient or other family members.
- The potential benefits of testing outweigh the potential risks.
• Testing is voluntary.
• The individual seeking testing or their legal proxy can provide informed consent.

Select Health of South Carolina considers the use of genetic testing for immunohistochemistry (IHC) or for micro-satellite instability (MSI) prior to testing for the germ line mutations (e.g., MLH1, MSH2, MSH6, and others) for tumors associated with Lynch syndrome (including uterine endometrial carcinoma acquired at age < 50 years) to be clinically proven and, therefore, medically necessary in members who meet the following criteria:

• Colorectal cancer is diagnosed at age < 50 years.
• Synchronous or metachronous colorectal or other tumors related to Lynch syndrome are diagnosed at any age.
• Tumor histology reveals tumor-infiltrating lymphocytes, Crohn’s-like lymphocytic reaction, mucinous or signet-ring differentiation, or medullary growth pattern at age < 60 years.
• Colorectal cancer is diagnosed where one or more first-degree relatives has tumors related to Lynch syndrome diagnosed at age < 50 years.
• Colorectal cancer is diagnosed where two or more first- or second-degree relatives has tumors related to Lynch syndrome diagnosed at any age.

OR

Each of the following criteria are fulfilled:

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

Limitations:

All other uses of genetic testing for hereditary cancer susceptibility are not medically necessary.

Alternative covered services:

• Primary care evaluation and diagnosis.
• Laboratory examination.
• Radiologic examination.

Background
The merits of genetic testing for hereditary cancer susceptibility are many, from early detection and prevention strategies to tailored therapy based on the genomic characteristics of the tumor itself.

Traditionally, families with multiple members who have an unusual pattern or number of cancers or tumors have been first evaluated clinically, although the investigation must be relatively specific to determine the susceptibility of each individual. Selected individuals and family members are asked to complete questionnaires specific to the tumor of interest. In some instances this information is gathered during history-taking by the triaging health care worker or by physical examination by a physician specialist. In addition, relevant supportive etiologic risk factor information is documented through review of pathology specimens and genealogical records. Often, family members are also asked to donate biologic specimens to be used in the search for cancer etiology and mechanisms of carcinogenesis.

The development of next-generation sequencing techniques — including whole genome sequencing (WGS), whole exome sequencing (WES), and ribonucleic acid (RNA) sequencing — has significantly advanced the ability of investigators to query in a systematic fashion the molecular mechanisms underlying tumor formation. To date, more than 1,000 cancers ranging from hematologic malignancies to central nervous system (CNS) and non-CNS solid tumors have been successfully identified using these technologies without the laborious one-on-one data-collection that is often personally intrusive to a patient and yields a paucity of clinically relevant information.

Familial cancer syndromes for which heritable risk has been identified, and which are particularly notable in the population, occur among those patients suffering from colorectal cancer. Among the diagnoses familiar to well-defined risk of heritable disease in this group are:

- Lynch syndrome.
- Familial adenomatous polyposis.
- MutY human homolog-associated polyposis.
- Peutz-Jeghers disease.
- Juvenile polyposis.
- Serrated polyposis syndrome.

It has become clear that genomic approaches can accurately classify tumors into distinct pathologic and prognostic subtypes and detect alterations in cellular pathways that may serve as novel therapeutic targets. These studies suggest that by characterizing the genomic make-up of individual tumors, investigators will be able to develop personalized and potentially more effective cancer treatments and/or preventive measures. This testing is not without its limitations, though, and is only appropriate when reasonable individual cancer risk estimates can be delivered and for those participants who choose to know their individual genetic status after proper informed consent, patient education pertinent to the risk, and genetic counseling are in place and delivered as adjuncts to the testing results.

**Searches**
Select Health of South Carolina searched PubMed and the databases of:

- UK National Health Services Center for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on February 13, 2018. Searched terms were: "gene sequencing” (MeSH), "gene expression” (MeSH), and "genetic testing for hereditary cancer susceptibility."

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

There is a growing body of evidence regarding genetic testing for hereditary cancer susceptibility. Much of the available medical evidence to date has centered around study of individuals and families at high risk of cancer, and of selected tumors, to investigate the genetic susceptibility and environmental exposures which may alter cancer risk. As a rule, both genetic and environmental risk factor information specific for the tumor type is obtained to establish a risk score and prediction rubric for heritable susceptibility.

Hereditary cancer counseling, evaluation, and risk assessment are the topics of a comprehensive set of practice recommendations from the National Society of Genetic Counselors (NSGC 2014).

Among the recommended interventions and practices advocated by the group are:

- Personal medical history.
- Family medical history (three – four generations).
- Genetic cancer risk assessment.
- Genetic testing.
- Obtaining informed consent prior to genetic testing.
- Disclosure of genetic test results.
- Personalized interpretation of results.
- Psychological assessment.
NSGC believes, on the basis of the available medical evidence, that genetic testing for heritable cancer susceptibility should be offered when the following conditions apply:

- An individual has a personal or family history suggestive of an inherited cancer syndrome.
- The genetic test can be adequately interpreted.
- Testing will influence medical management of the patient or other family members.
- The potential benefits of testing outweigh the potential risks.
- Testing is voluntary.
- The individual seeking testing or their legal proxy can provide informed consent.

The Royal Australian College of General Practitioners guidelines (2012) for preventive activities in general practice were developed by a task force of general practitioners (GPs) and experts to identify patients who may potentially benefit from genetic testing for heritable cancer. The task force gives its strongest recommendation, based on the available medical evidence, to the practice of collecting a comprehensive family history from all patients at risk for hereditary malignancies, including first-degree or second-degree relatives, ideally extending to three generations, covering both sides of the family, and ethnic background. The task force recommends, based on the available medical evidence, that genetically determined cancers should be sought when the above indications are present, including:

- Breast and ovarian cancer.
- Colon cancer.

Lynch syndrome, previously referred to as hereditary nonpolyposis colorectal cancer syndrome (HNPCC), is the subject of guidelines issued by the American Gastroenterological Association (AGA) Clinical Guidelines Committee and approved by the AGA Governing Board (Rubenstein 2015). In patients without a personal history of colorectal or another Lynch-related cancer, but with a family history suggestive of Lynch syndrome, the AGA suggests that risk prediction models be offered rather than proceeding with genetic testing; however, the AGA accedes that there is very low-quality evidence to date for this practice. In patients with a history of colorectal cancer, the AGA cites moderate-quality evidence of benefit for either IHC or for MSI to identify potential cases of Lynch syndrome versus doing no testing for Lynch syndrome. The AGA also recommends surveillance colonoscopy every year or every other year in persons with known Lynch syndrome; and the AGA suggests that aspirin be offered for cancer prevention in patients with Lynch syndrome, though there is again low-quality evidence at this time for the practice.

The guidelines of the National Comprehensive Cancer Network (NCCN 2015) recommend that, where a familial colorectal cancer mutation is known, genetic testing for that mutation be carried out as a screening examination in family members. In the absence of known familial mutation, testing for Lynch syndrome may be offered with IHC or MSI after appropriate pretest counseling is performed. The NCCN follows the widely-disseminated Bethesda and Amsterdam criteria (Appendix A) for determining risk sufficient for testing, inclusive of those patients who have a family history of Lynch syndrome or are diagnosed with uterine endometrial cancer prior to the age of 50 years.
In a subsequent update specific to individuals diagnosed with colorectal carcinoma (NCCN, 2016), the body further advised:

- Lynch syndrome screening should be performed for all patients with colorectal cancer diagnosed at age ≤ 70 years.
- Lynch syndrome screening should also be performed for all patients with colorectal cancer age ≥ 70 years who meet the Bethesda guidelines.

The NCCN 2016 guidelines are issued with a Category 2A proviso: they are based upon lower-level evidence where there is uniform consensus that the intervention is appropriate.

If abnormal results are found for IHC and/or MSI, germline Lynch syndrome genetic testing may include testing for the following and other MMR mutations:

- MLH1.
- MSH2.
- MSH6.
- PMS2.
- EPCAM.
- MYH.

A systematic review (Hilgart 2012) included eight trials (10 papers) which covered the process of risk assessment for familial breast cancer. These focused on the psychosocial impact on patients, as well as other outcomes and aspects of service delivery, and provided data on 1,973 participants. Due to the limited number of trials, this review found insufficient evidence to make any firm conclusions about the best way to deliver risk-assessment services for individuals concerned about a family history of breast cancer. All eight included studies did, however, demonstrate improvements in psychological well-being and a decrease in the levels of cancer worry as a result of the risk-assessment service. Although limited, the findings of this review suggest that cancer genetic risk-assessment services can help to reduce distress, improve the accuracy of the individual's perceived risk of breast cancer, and increase knowledge about breast cancer and genetics. Existing evidence suggests that such services do not cause patients any harm and, in the short term, can have a positive effect by helping to ease distress and decrease cancer worry. From this review, it does not appear that the health professional delivering the risk assessment has a significant impact on these outcomes.

A cost-effectiveness analysis (Robson 2010) on behalf of the American Society of Clinical Oncologists (ASCO) has suggested that a threshold of greater than 5 percent predicted probability of carrying a Lynch syndrome mutation should prompt germline genetic testing if universally applied to 25-year-old patients. However, the threshold could be lower in middle-aged adults and, as the cost of genetic testing decreases, the marginal benefit of testing should be further enhanced. If the probability is above the threshold, then germline genetic testing for mutations in MLH1, MSH2, MSH6, and PMS2 should be offered.
A cost-effectiveness model (Quillin 2010) estimating life expectancy and health care costs of frequent colonoscopy surveillance versus no surveillance determined that surveillance of people who are gene carriers for Lynch syndrome increased life expectancy by seven years, and costs of surveillance were less than costs of no surveillance for colorectal cancer.

Policy updates:

A systematic review (Willis 2016) examining barriers to accessing genetic counseling (GC) found that, with the exceptions of education level, socioeconomic status, cancer-specific distress, personal cancer diagnosis, and actual and perceived risk of cancer, support was lacking for most sociodemographic, clinical, and psychosocial factors as predictors of GC engagement. Cost and logistical barriers, emotional concerns, family concerns, and low perceived personal relevance were reported as important considerations for those declining GC. The authors concluded that there is poor understanding of GC and a lack of decision support among those referred to GC. Research into ways of providing education and support was cited as important to advance the scope and availability of responsible genetic testing and follow-on GC.

During the past twelve months there has been further information published regarding genetic testing for hereditary cancer susceptibility.

A retrospective review (Romero-Arenas 2018) found patients (n=312) believe it is important for physicians to inform them of potentially beneficial developments in genetic testing. However, physician-initiated letters to introduce new information appear inadequate alone in motivating patients to seek additional genetic counseling and testing. Ninety-seven of 312 (31.1 percent) eligible patients with an identified mailing address were sent a questionnaire assessing behaviors and attitudes with regard to genetic information and testing. After receiving the letter, 29.2 percent patients discussed genetic testing with their doctor, 39.3 percent considered pursuing genetic testing, and 8.5 percent underwent testing. Nearly all respondents (97 percent) indicated that physicians should inform patients about new developments that may improve their or their family's health, and 71 percent thought patients shared this responsibility. Most patients understood the letter (84 percent) and were pleased it was sent (84 percent), although 11 percent found it upsetting.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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| Romero (2018) Recontacting Patients with Updated Genetic Testing Recommendations for Medullary Thyroid | Key points:  
- Retrospective review found patients (n=312) believe it is important for physicians to inform them of potentially beneficial developments in genetic testing.  
- However, physician-initiated letters to introduce new information appear inadequate alone in motivating patients to seek additional genetic counseling and testing.  
- Ninety-seven of 312 (31.1%) eligible patients with an identified mailing address were sent a |
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| Carcinoma and Pheochromocytoma or Paraganglioma.                      | questionnaire assessing behaviors and attitudes with regard to genetic information and testing.  
  - After receiving the letter, 29.2% patients discussed genetic testing with their doctor, 39.3% considered pursuing genetic testing, and 8.5% underwent testing.  
  - Nearly all respondents (97%) indicated that physicians should inform patients about new developments that may improve their or their family's health, and 71% thought patients shared this responsibility.  
  - Most patients understood the letter (84%) and were pleased it was sent (84%), although 11% found it upsetting. |
| Willis (2016)                                                          | **Key points:**  
  - Systematic review found support was lacking for most sociodemographic, clinical, and psychosocial factors as predictors of GC engagement.  
  - Cost and logistical barriers, emotional concerns, family concerns, and low perceived personal relevance were reported as important considerations for those declining GC.  
  - The authors concluded that there is poor understanding of GC and a lack of decision support among those referred to GC. |
| Riley (2010)                                                           | **Key points:**  
  - Practice guidelines for hereditary cancer counseling, evaluation, and risk assessment.  
  - Among the recommended interventions and practices advocated by the group are:  
    o Personal medical history.  
    o Family medical history (three – four generations).  
    o Genetic cancer risk assessment.  
    o Genetic testing.  
    o Obtaining informed consent prior to genetic testing.  
    o Disclosure of genetic test results.  
    o Personalized interpretation of results.  
    o Psychological assessment.  
  - NSGC concluded on the basis of available medical evidence that genetic testing for heritable cancer susceptibility should be offered when the following conditions apply:  
    o An individual has a personal or family history suggestive of an inherited cancer syndrome.  
    o The genetic test can be adequately interpreted.  
    o Testing will influence medical management of the patient or other family members.  
    o The potential benefits of testing outweigh the potential risks.  
    o Testing is voluntary.  
    o The individual seeking testing or their legal proxy can provide informed consent. |
| Royal Australian College of General Practitioners (2012)               | **Key points:**  
  - Practice guidelines to identify patients who may potentially benefit from genetic testing for heritable cancer.  
  - Strongest recommendation:  
    o Comprehensive family history from all patients at risk for hereditary |
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<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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| NCCN (2016) | Malignancies including first-degree or second-degree relatives, ideally extending to three generations, covering both sides of the family and ethnic background.  
- Moderate recommendation:  
  o Genetically determined cancers should be sought when the above indications are present, including:  
    ▪ Breast and ovarian cancer.  
    ▪ Colon cancer. |
| Rubenstein (2015) | **Key points:**  
- Lynch syndrome screening should be performed for all patients with colorectal cancer diagnosed at age ≤ 70 years.  
- Lynch syndrome screening should also be performed for all patients with colorectal cancer ≥ 70 years of age who meet the Bethesda guidelines. |
| NCCN (2015) | **Key points:**  
- Practice guidelines for patients with a family history suggestive of Lynch syndrome:  
  o Low-quality evidence for:  
    ▪ Risk prediction models rather than proceeding with genetic testing.  
    ▪ Aspirin therapy for cancer prevention in patients with Lynch syndrome.  
  o Moderate-quality evidence for:  
    ▪ IHC or MSI to identify potential cases of Lynch syndrome versus doing no testing for Lynch syndrome. |
| Hilgart (2012) | **Key points:**  
- Systematic review (1,973 subjects) included eight trials (10 papers) that examined risk assessment for familial breast cancer and its psychosocial impact on patients.  
- The review found insufficient evidence to make any firm conclusions for individuals concerned about a family history of breast cancer.  
- All studies demonstrated improvements in psychological well-being and a decrease in the levels of cancer worry as a result of the risk-assessment service.  
- The authors concluded that existing evidence suggests that such services do not cause patients any harm and, in the short term, can have a positive effect by helping to ease distress and decrease cancer worry. |
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| Robson (2010) ASCO policy statement update: genetic and genomic testing for cancer susceptibility | Key points:  
- Cost-effectiveness study:  
  - A threshold of greater than 5% predicted probability of carrying a Lynch syndrome mutation should prompt genetic testing for mutations in MLH1, MSH2, MSH6, and PMS2. |
| Quillen (2010) Exploring hereditary cancer among dying cancer patients — a cross-sectional study of hereditary risk and perceived awareness of DNA testing and banking | Key points:  
- Cost-effectiveness model:  
  - Life expectancy and health care costs of frequent colonoscopy determined that surveillance of people who are gene carriers for Lynch syndrome increased life expectancy by seven years.  
  - Costs of surveillance were less than costs of no surveillance for colorectal cancer. |

**References**

**Professional society guidelines/other:**


**Peer-reviewed references:**


**CMS National Coverage Determination (NCDs):**

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**

Multiple LCDs were identified as of the writing of this policy: CMS website. [https://www.cms.gov/medicare-coverage-database/search/search-](https://www.cms.gov/medicare-coverage-database/search/search-)
Commonly submitted codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Comments</th>
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<tbody>
<tr>
<td>81292</td>
<td>MLH1 (muhtL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
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<tr>
<td>81294</td>
<td>MLH1 (muhtL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
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<tr>
<td>81295</td>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
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<tr>
<td>81297</td>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
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<tr>
<td>91298</td>
<td>MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
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<tr>
<td>81300</td>
<td>MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
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<tr>
<td>81317</td>
<td>PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
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<tr>
<td>81319</td>
<td>PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
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<tr>
<td>81403</td>
<td>Molecular pathology procedure, Level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of &gt;10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)</td>
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<tr>
<th>ICD-10 Code</th>
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<tbody>
<tr>
<td>C18.0</td>
<td>Malignant neoplasm of cecum</td>
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<tr>
<td>C18.1</td>
<td>Malignant neoplasm of appendix</td>
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<tr>
<td>C18.2</td>
<td>Malignant neoplasm of ascending colon</td>
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<td>C18.3</td>
<td>Malignant neoplasm of hepatic flexure</td>
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<td>C18.4</td>
<td>Malignant neoplasm of transverse colon</td>
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<td>ICD-10 Code</td>
<td>Description</td>
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<tr>
<td>C18.5</td>
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<td>C18.6</td>
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<td>C18.8</td>
<td>Malignant neoplasm of overlapping sites of colon</td>
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<td>C18.9</td>
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<td>C19</td>
<td>Malignant neoplasm of rectosigmoid junction</td>
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<td>C54.1</td>
<td>Malignant neoplasm of endometrium</td>
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<td>K63.5</td>
<td>Polyp of colon</td>
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<td>Family history of malignant neoplasm of digestive organs</td>
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<td>Family history of colonic polyps</td>
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<td>Z85.048</td>
<td>Personal history of other malignant neoplasm of rectum, rectosigmoid junction, and anus</td>
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<td>Z86.010</td>
<td>Personal history of colonic polyps</td>
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**Appendix A**

**Bethesda guidelines:**

Criteria are as follows:

- Colorectal cancer is diagnosed at age < 50 years.
- Synchronous or metachronous colorectal or other tumors related to Lynch syndrome are diagnosed at any age.
- Tumor histology reveals tumor-infiltrating lymphocytes, Crohn’s-like lymphocytic reaction, mucinous or signet-ring differentiation, or medullary growth pattern at age < 60 years.
- Colorectal cancer is diagnosed where one or more first-degree relatives has tumors related to Lynch syndrome diagnosed at age < 50 years.
- Colorectal cancer is diagnosed where two or more first- or second-degree relatives has tumors related to Lynch syndrome diagnosed at any age.

**Amsterdam guidelines:**

Each of the following criteria must be fulfilled:

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