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: May 19, 2017
Next Review Date: May 2018

Related policies:

CP# 02.01.02 Genetic testing for breast and ovarian cancer
CP# 02.01.08 Familial polyposis gene testing
CP# 02.01.09 Genetic testing, rare diseases
CP# 02.01.10 COLARIS® testing for Lynch syndrome

ABOUT THIS POLICY: AmeriHealth Caritas has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas’ 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 AmeriHealth Caritas when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas’ 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. AmeriHealth Caritas’ clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas will update its clinical policies as necessary. AmeriHealth Caritas’ clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas considers the use of genetic testing for hereditary cancer susceptibility to be clinically proven and, therefore, medically necessary when the following criteria are met:

- 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.

AmeriHealth Caritas considers the use of genetic testing for immunohistochemistry (IHC) or for microsatellite 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**

AmeriHealth Caritas 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 March 27, 2017. 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 (Appendix A) 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.

Hayes (2005) also has evaluated the potential of genetic testing for diagnosis of Lynch syndrome and concludes that in families with suspected or clinically frank Lynch syndrome, genetic testing for mutations in one of several mismatch repair (MMR) genes may be useful to determine whether an individual has an increased risk for colorectal cancer or other HNPCC-associated cancers. Hayes acknowledges that improving cancer risk assessment in these individuals and families may be beneficial and cites MSI analysis and/or IHC staining of the tumor tissue of an affected family member as an initial screening test before germline mutation testing is performed.

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 cancer associated with Lynch syndrome. Those found to have an MMR mutation may also benefit from enhanced surveillance and prophylactic treatments. Other cancers that
have been linked to Lynch syndrome mutations include gastric cancer and cancer of the small intestine.

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 B) 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.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tr>
<td>Willis (2016)</td>
<td>Key points:</td>
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<td>Sociodemographic,</td>
<td>Systematic review found support</td>
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<td>psychosocial and</td>
<td>was lacking for most sociodemographic, clinical, and</td>
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<td>to advance the scope and availability of responsible genetic testing and follow-on GC.</td>
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<tr>
<td>Riley (2010)</td>
<td>Key points:</td>
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<td>Essential elements</td>
<td>Practice guidelines for hereditary</td>
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<td>of</td>
<td>cancer counseling, evaluation, and</td>
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<td>risk assessment.</td>
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<tr>
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<td>Content, Methods, Recommendations</td>
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| Genetic cancer risk assessment, counseling, and testing: updated recommendations of the NSGC | - 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) Genetic counselling and testing | 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 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. |
| NCCN (2016) NCCN Guidelines Version 2.2016 Updates Colon Cancer | 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 (Appendix A). |
| Rubenstein (2015) AGA guidelines on the diagnosis and management of | 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.  
<table>
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<th>Content, Methods, Recommendations</th>
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| Lynch syndrome. | Moderate-quality evidence for:  
  - IHC or MSI to identify potential cases of Lynch syndrome versus doing no testing for Lynch syndrome. |
| NCCN (2015) | **Key points:**  
  - Practice guidelines recommend:  
    - Where a familial colorectal cancer mutation is known, genetic testing for that mutation should be ordered.  
    - In the absence of known familial mutation, testing for Lynch syndrome may be offered with IHC or MSI after appropriate pretest counseling.  
    - The NCCN follows Bethesda and Amsterdam criteria 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 age 50 years. |
| Hayes (2005) | **Key points:**  
  - Genetic testing may be used to determine whether an individual has an increased risk for colorectal cancer or other HNPCC-associated cancers.  
  - MSI analysis and/or IHC staining may be beneficial as an initial screening test before germline mutation testing is performed. |
| 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. |
| Robson (2010) | **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. |
| Quillin (2010) | **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. |
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<td>perceived awareness of DNA testing and banking</td>
<td>cancer.</td>
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**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-results.aspx?CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=Genetic+testing&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAAAAAA%3d%3d&=&](https://www.cms.gov/medicare-coverage-database/search/search-results.aspx?CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=Genetic+testing&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAAAAAA%3d%3d&=&). Accessed March 27, 2017.

**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>
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<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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<td>81294</td>
<td>MLH1 (mutL 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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<td>81295</td>
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<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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<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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<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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<td>C18.0</td>
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<td>C18.4</td>
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<td>C18.5</td>
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<td>Z85.048</td>
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**Appendix A**

Computer models have been developed to assess the likelihood that a patient carries a mutation in a MMR gene:

- PREMM (available online at premm.dfci.harvard.edu/).
- MMR Predict (available online at hnpccpredict.hgu.mrc.ac.uk/).
- MMRpro (available online at www4.utsouthwestern.edu/breasthealth/cagene).

**Appendix B**

**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.