Genetic Testing for Hereditary Colorectal and Uterine Cancer

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Disclaimer
The Coverage Summaries are reviewed by the iCare Medicare Utilization Management Committee. Policies in this document may be modified by a member’s coverage document. Clinical policy is not intended to preempt the judgment of the reviewing medical director or dictate to health care providers how to practice medicine. Health care providers are expected to exercise their medical judgment in rendering appropriate care. Identification of selected brand names of devices, tests and procedures in a medical coverage policy is for reference only and is not an endorsement of any one device, test, or procedure over another. Clinical technology is constantly evolving, and we reserve the right to review and update this policy periodically. References to CPT® codes or other sources are for definitional purposes only and do not imply any right to reimbursement or guarantee of claims payment. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any shape or form or by any means, electronic, mechanical, photocopying or otherwise, without permission from iCare.

Related Medicare Advantage Medical/Pharmacy Coverage Policies

Genetic Testing
Genetic Testing for Hereditary Breast, Ovarian, Pancreatic and Prostate Cancer
Genetic Testing for Hereditary Cancer

Related Documents

Please refer to CMS website for the most current applicable CMS Online Manual System (IOMs)/National Coverage Determination (NCD)/ Local Coverage Determination (LCD)/Local Coverage Article (LCA)/ Transmittals.
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**LCD**

**LCA**

AK, AZ, ID, MT, ND, OR, SD, UT, WA, WY

**JF - Noridian Healthcare Solutions, LLC**

AR, CO, NM, OK, TX, LA, MS

**JJ, JM - Palmetto GBA**

AL, GA, NC, SC, TN, VA, WV
Genetic testing is a laboratory method that is performed to analyze an individual’s deoxyribonucleic acid (DNA) to detect gene variants (mutations) associated with inherited conditions including hereditary cancer such as colorectal and uterine cancer. Testing may be appropriate for affected individuals as well as asymptomatic family members at increased risk for cancer. This type of testing may also be referred to as germline genetic testing. Genetic testing is available for a variety of inherited colorectal cancer (CRC) syndromes which can be categorized as nonpolyposis (absence of polyps) or polyposis (presence of numerous polyps). Testing is available for familial adenomatous polyposis (FAP), Lynch syndrome, MUTYH-associated polyposis (MAP) and Peutz-Jeghers syndrome (PJS).

Multigene (or expanded) panels analyze a broad set of genes simultaneously (as opposed to single gene testing that searches for variants in one specific gene) and have been proposed to evaluate the DNA of an individual with a personal and/or family history of more than one hereditary condition or syndrome or hereditary conditions/syndromes associated with more than one gene. Panels often include medically actionable genes but may also include those with unclear medical management. Targeted (or focused) multigene panels analyze a limited number of genes targeted to a specific condition.

Coverage Determination

*iCare follows the CMS requirements that only allows coverage and payment for services that are reasonable and necessary for the diagnosis and treatment of illness or injury or to improve the functioning of a malformed body member except as specifically allowed by Medicare.*

Genetic tests must demonstrate clinical utility, analytical and clinical validity and fulfill the CMS “reasonable and necessary” criteria. Analytic validity (test accurately identifies the gene variant), clinical validity (test identifies or predicts the clinically defined disorder) and clinical utility (test measurably improves clinical outcomes) of the genetic test is supported by generally accepted standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, specialty society recommendations, and views of physicians practicing in relevant clinical areas. The test must be ordered by a physician who is treating the beneficiary and the results will be used in the management of a beneficiary’s specific medical problem.
For jurisdictions with no Medicare guidance for a particular test, iCare will utilize the MolDX program and Technical Assessments for molecular assays as the standard to evaluate clinical utility, analytical and clinical validity in conjunction with adhering to Medicare’s reasonable and necessary requirement.

In interpreting or supplementing the criteria above and in order to determine medical necessity consistently, iCare may consider the following criteria:

**LYNCH SYNDROME**

**Lynch Syndrome Tumor Screening and Genetic Testing General Criteria**

Lynch syndrome tumor screening and genetic testing will be considered medically reasonable and necessary when the following requirements are met:

- Personal history of a Lynch syndrome-related cancer (colorectal, endometrial, gastric ovarian, pancreatic, urothelial, brain [usually glioblastoma], biliary tract, small intestine, sebaceous adenomas, sebaceous carcinomas and keratoacanthomas) and any of the following:
  - Has an affected first-, second- or third-degree relative with a pathogenic or likely pathogenic variant. (Genetic testing should be limited to the known familial variant [KFV]);\(^{20,81}\) OR
  - Has an affected first-, second- or third-degree relative with a Lynch syndrome-related cancer diagnosed at any age;\(^{81}\) OR
  - Has a close family member (first- or second-degree relative) with a Lynch syndrome-related cancer diagnosed at any age;\(^{81}\) OR
  - Has a close family history with at least two first- or second-degree relatives on the same side of the family with Lynch syndrome-related cancers diagnosed at any age;\(^{81}\) OR
  - Has a calculated risk assessment score for Lynch syndrome (PREMMS) score of greater than equal to 2.5%);\(^{81}\) OR

- Diagnosed at any age with an MMR deficient Lynch syndrome-related cancer (colorectal, endometrial, gastric ovarian, pancreatic, urothelial, brain [usually glioblastoma], biliary tract, small intestine, sebaceous adenomas, sebaceous carcinomas and keratoacanthomas);\(^{81}\) OR
• Personal history of a tumor diagnosed at any age that has been tested and found to have a pathogenic or likely pathogenic variant associated with Lynch syndrome

**DNA Mismatch Repair by Immunohistochemistry**

Lynch syndrome tumor testing for DNA mismatch repair (MMR) by qualitative immunohistochemistry (IHC) will be considered medically reasonable and necessary when the following requirements are met:

- Individual meets Lynch Syndrome Tumor Screening and Genetic Testing General Criteria; AND
- IHC has not previously been performed on the individual’s tumor sample

**Microsatellite Instability Tumor Testing**

*Microsatellite instability (MSI) tumor testing* will be considered medically reasonable and necessary when the following requirements are met:

- Individual meets Lynch Syndrome Tumor Screening and Genetic Testing General Criteria; AND
- MSI has not previously been performed on the individual’s tumor sample; AND
- Results of IHC testing is normal

*MSI may be performed by polymerase chain reaction (PCR) or by multigene NGS panel inclusive of MSI microsatellite loci and MLH1, MSH2, MSH6, PMS2 and EPCAM genes. Refer to Limitations section.

**BRAF Gene Analysis**

*BRAF gene analysis* will be considered medically reasonable and necessary when the following requirements are met:

- Individual meets Lynch Syndrome Tumor Screening and Genetic Testing General Criteria; AND
- IHC indicates loss of MLH1 protein expression

**MLH1 Promoter Methylation Testing**

*MLH1 promoter methylation testing* will be considered medically reasonable and necessary when the following requirements are met:

- Individual meets Lynch Syndrome Tumor Screening and Genetic Testing General Criteria; AND
- IHC indicates loss of MLH1 protein expression; AND
- BRAF gene analysis is negative

**Single Gene Sequencing and Deletion/Duplication Analysis**

Single gene sequencing and deletion/duplication analysis will be considered medically reasonable and necessary when the following requirements are met:
• Individual meets Lynch Syndrome Tumor Screening and Genetic Testing General Criteria; AND
  o MLH1 gene analysis when the following are present:
    ▪ MLH1 promoter is hypermethylated; OR
    ▪ MLH1 promoter is normally methylated and BRAF is negative
  o MSH2 gene analysis when IHC shows loss of MSH2 and MSH6
  o MSH6 gene analysis when the following are present:
    ▪ IHC shows loss of MSH6; OR
    ▪ MLH1 and MSH2 gene analysis is negative; OR
    ▪ EPCAM deletion analysis is negative
  o PMS2 gene analysis when the following are present:
    ▪ IHC shows a loss of PMS2 only; OR
    ▪ MSH6 gene analysis is negative
  o EPCAM deletion analysis when MSH2 germline genetic testing is negative

**Multigene Next-Generation Sequencing Panel Testing for Lynch Syndrome**

Multigene next-generation sequencing (NGS) panel testing will be considered medically reasonable and necessary when the following requirements are met:

• Individual meets Lynch Syndrome Tumor Screening and Genetic Testing General Criteria; AND
  o Normal IHC and MSI high (MSI-H) results; OR
  o Tumor is not available, or a pathologist has determined to be inadequate to assess DNA MMR deficiency by MSI or IHC; OR
  o Tumor sample no longer available; AND

• Requirements of NCD 90.2 Section B2 have been met; AND

• Test is FDA approved/cleared; AND

• Analytic validity, clinical validity and clinical utility of the genetic test is supported by the MolDX program; AND

• All genes in the panel are relevant to the personal and family history for the individual being tested
FAMILIAL ADENOMATOUS AND HAMARTOMATOUS POLYPOSIS SYNDROMES

Familial Adenomatous and Hamartomatous Polyposis Syndrome Genetic Testing General Criteria

Genetic testing for familial adenomatous and hamartomatous polyposis syndrome (familial adenomatous polyposis [FAP], attenuated FAP [AFAP], MUTYH-associated polyposis [MAP], Peutz Jeghers syndrome [PJS]) will be considered medically reasonable and necessary when the following requirements are met (based on NCCN guidelines category 1 or 2A recommendations).81

- Personal history of any of the following:
  - 2 or more histologically confirmed PJS-type hamartomatous polyps; OR
  - 2 or more polyps 10 millimeters or more in size; OR
  - 5 or more serrated lesions or polyps proximal to the rectum and all polyps 5 millimeters or more in size with at least 2 being at least 10 millimeters; OR
  - 10 or more adenomas during the lifetime; OR
  - 20 or more serrated lesions or polyps of any size distributed throughout the large bowel, with 5 or more being proximal to the rectum; OR
  - Congenital hypertrophy of retinal pigment epithelium (CHRPE) (unilateral, bilateral or multifocal); OR
  - Cribriform-morular variant of papillary thyroid cancer; OR
  - Desmoid tumor; OR
  - Hepatoblastoma; OR
  - Perioral or buccal hyperpigmentation; OR

- Is affected and has a first-, second- or third-degree relative with a pathogenic or likely pathogenic variant in a familial adenomatous and hamartomatous polyposis syndromes gene (Genetic testing should be limited to the KFV)

Single Gene Sequencing and Deletion/Duplication Analysis (APC, MUTYH, STK11)

Single gene sequencing and deletion/duplication analysis (APC, MUTYH, STK11) will be considered medically reasonable and necessary for familial adenomatous and hamartomatous polyposis syndrome when the individual meets Familial Adenomatous and Hamartomatous Polyposis Syndrome Genetic Testing General Criteria.

Multigene Next-Generation Sequencing Panel Testing for Familial Adenomatous and Hamartomatous Polyposis Syndrome
Multigene next-generation sequencing (NGS) panel testing will be considered medically reasonable and necessary when the following requirements are met:

- Individual meets Familial Adenomatous and Hamartomatous Polyposis Syndrome Genetic Testing General Criteria; AND
- Requirements of NCD 90.2 Section B2 have been met; AND
- Test is FDA approved/cleared; AND
- Analytic validity, clinical validity and clinical utility of the genetic test is supported by the MolDX program; AND
- All genes in the panel are relevant to the personal and family history for the individual being tested

The use of the criteria in this Medicare Advantage Medical Coverage Policy provides clinical benefits highly likely to outweigh any clinical harms. Services that do not meet the criteria above are not medically necessary and thus do not provide a clinical benefit. Medically unnecessary services carry risks of adverse outcomes and may interfere with the pursuit of other treatments which have demonstrated efficacy.

Coverage Limitations

US Government Publishing Office, Electronic code of federal regulations: part 411 – 42 CFR § 411.15 - Particular services excluded from coverage

The following tests may not be considered a benefit (statutory exclusion): 85

- Tests considered screening in the absence of clinical signs and symptoms of disease that are not specifically identified by the law; OR
- Tests that confirm a diagnosis or known information; OR
- Tests to determine risk for developing a disease or condition; OR
- Tests performed to measure the quality of a process; OR
- Tests without diagnosis specific indications; OR
- Tests identified as investigational by available literature and/or the literature supplied by the developer and are not a part of a clinical trial

These treatments and services fall within the Medicare program’s statutory exclusion that prohibits payment for items and services that have not been demonstrated to be reasonable and necessary for the
diagnosis and treatment of illness or injury (§1862(a)(1) of the Act). Other services/items fall within the Medicare program’s statutory exclusion at 1862(a)(12), which prohibits payment.

The following items will not be considered medically reasonable and necessary:

- Any laboratory test that investigates the same germline genetic content, for the same genetic information, that has already been tested in the same individual²⁵,²⁶,²⁷,²⁸,²⁹
- Deletion/duplication analysis is obtained as part of the sequencing procedure but submitted as an independent analysis
- Genetic tests that have not demonstrated clinical utility, analytical and clinical validity via the MolDX Program
- MSI analysis is obtained as part of a multigene NGS panel but submitted as an independent analysis¹⁴,¹⁵,¹⁶
- Multigene panel if only a single gene on the panel is considered reasonable and necessary
- Multigene panel with genes that are not relevant to the individual’s personal and family history
- Multigene panel used to confirm a variant(s) detected by somatic tumor testing that can be confirmed by a test targeted to that specific variant(s)²⁵,²⁶,²⁷,²⁸,²⁹
- Multigene panel used to identify a KFV that could be identified with a test targeted to that specific variant²⁵,²⁶,²⁷,²⁸,²⁹
- Repeat germline testing (testing is limited to once-in-a-lifetime)³⁵,³⁶,³⁷,³⁸,³⁹

A review of the current medical literature shows that the evidence is insufficient to determine that these services are standard medical treatments. There remains an absence of randomized, blinded clinical studies examining benefit and long-term clinical outcomes establishing the value of these services in clinical management.

**Coding Information**

Any codes listed on this policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and/or reimbursement for a service or procedure.
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<td>MSH6 (mutS homolog 6) (eg, hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)</td>
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<tr>
<td>0162U</td>
<td>Hereditary colon cancer (Lynch syndrome), targeted mRNA sequence analysis panel (MLH1, MSH2, MSH6, PMS2) (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>0238U</td>
<td>Oncology (Lynch syndrome), genomic DNA sequence analysis of MLH1, MSH2, MSH6, PMS2, and EPCAM, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions</td>
</tr>
</tbody>
</table>

CPT®

No code(s) identified

HCPCS Code(s)

No code(s) identified
References


Appendix

Appendix A
Family Relationships

<table>
<thead>
<tr>
<th>Degree of Relationship</th>
<th>Relative of the Individual to be Tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-degree</td>
<td>Child, full-sibling, parent</td>
</tr>
<tr>
<td>Second-degree</td>
<td>Aunt, uncle, grandchild, grandparent, nephew, niece, half-sibling</td>
</tr>
<tr>
<td>Third-degree</td>
<td>First cousin, great aunt, great-uncle, great-grandchild, great-grandparent, half-aunt, half-uncle</td>
</tr>
</tbody>
</table>

Change Summary
- 01/01/2024 New Policy.