



GENETIC TESTING FOR HEREDITARY NON-POLYPOSIS COLORECTAL CANCER (HNPCC) HS-154



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Genetic Testing for Hereditary Non-Polyposis Colorectal Cancer (HNPCC)

Policy Number: HS-154

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DISCLAIMER

The Clinical Coverage Guideline is intended to supplement certain standard WellCare benefit plans. The terms of a member's particular Benefit Plan, Evidence of Coverage, Certificate of Coverage, etc., may differ significantly from this Coverage Position. For example, a member's benefit plan may contain specific exclusions related to the topic addressed in this Clinical Coverage Guideline. When a conflict exists between the two documents, the Member's Benefit Plan always supersedes the information contained in the Clinical Coverage Guideline. Additionally, Clinical Coverage Guidelines relate exclusively to the administration of health benefit plans and are NOT recommendations for treatment, nor should they be used as treatment guidelines. The application of the Clinical Coverage Guideline is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations and state-specific Medicaid mandates, if any.

APPLICATION STATEMENT

The application of the Clinical Coverage Guideline is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations and state-specific Medicaid mandates, if any.

BACKGROUND

Hereditary nonpolyposis colorectal cancer (HNPCC) is one of several familial syndromes that is associated with a high risk of colorectal adenocarcinoma. HNPCC is an autosomal dominant condition that is characterized by young age of onset (mean age 44 years), proximal colon location of tumors, multiple primary cancers, and increased risk of endometrial, small bowel, gastric, bile duct, and ovarian cancers, as well as transitional cell cancer of the ureters. The most common extracolonic malignancy is endometrial adenocarcinoma. Germline mutations in one of several mismatch repair (MMR) genes cause HNPCC; these MMR genes include *hMSH2*, *hMLH1*, *hPMS1*, *hPMS2*, *hMSH3*, and *hMSH6*. While at least six of these genes have been implicated in the occurrence of HNPCC, the genes *hMSH2* and *hMLH1* are thought to account for the majority of mutations of the MMR genes found in families with HNPCC. Colorectal tumor deoxyribonucleic acid (DNA) from individuals with HNPCC usually shows a high level of microsatellite instability (MSI-H); tumor DNA that exhibits alterations in microsatellite regions (these are repeating sequences of bases found throughout the genome) indicates probable defects in MMR genes.

Lifetime risk of colorectal cancer for individuals with HNPCC has been estimated at 80% by age 75, and there is a 60% lifetime risk of endometrial cancer. Recommended surveillance for mutation carriers is annual colonoscopy beginning at the age of 25. In families in which there is a pattern of occurrence of extracolonic cancers, particularly endometrial cancer, surveillance options include yearly Pap smears, pelvic exams, urine cytology, esophagogastroduodenoscopy, pelvic ultrasound, and endometrial biopsy.

Germline genetic testing for mutations in *hMSH2* and *hMLH1*, and more recently in *hMSH6*, is now being offered by several commercial laboratories. Genetic testing serves two primary purposes in the management of individuals with suspected or clinically diagnosed HNPCC: (1) confirmation of the diagnosis in a suspected proband that may exhibit classic or atypical clinical features; and (2) risk assessment in presymptomatic family members (Hayes, 2005).

Microsatellite Instability (MSI)

Microsatellite instability (MSI) is found in the colorectal cancer DNA (but not in the adjacent normal colorectal mucosa) of most individuals with germline mismatch repair gene mutations. In combination with immunohistochemistry for MSH2 and MLH1, MSI testing using the Bethesda markers should be performed on the tumor tissue of individuals putatively affected with HNPCC. A result of MSI-high in tumor DNA usually leads to consideration of germline testing for mutations in the MSH2 and MLH1 genes. Individuals with MSI-low or microsatellite stable (MSS) results are unlikely to harbor mismatch repair gene mutations, and further genetic testing is usually not pursued.

POSITION STATEMENT

Genetic testing for hereditary non-polyposis colorectal cancer (HNPCC; MLH1, MSH2, MSH6, PMS2 sequence analysis) **is considered medically necessary** if the following criteria are met:

- Member meets Amsterdam II criteria or revised Bethesda guidelines (see below); **OR**,
- Member has a first or second degree relative with a disease causing HNPCC mutation (genes MLH1, MSH2, MSH6, PMS2)

AND,

- The results of the genetic test will impact treatment course for the member.

NOTE: Microsatellite instability (MSI) testing is considered medically necessary as an initial test in members with colorectal cancer who meet the revised Bethesda criteria (see below) in order to identify those persons who should proceed with HNPCC mutation analysis.

Amsterdam II Criteria:

At least three relatives must have an HNPCC-related cancer*, and ALL of the following criteria must be met:

- One must be a first-degree relative of the other two: **AND**,
- At least two successive generations must be affected; **AND**,
- At least one of the relatives with cancer associated with HNPCC should be diagnosed before the age of 50 years; **AND**,
- Familial adenomatous polyposis (FAP) should be excluded in the colorectal cancer cases (in any); **AND**,
- Tumors should be verified whenever possible.

Revised Bethesda Criteria:

- Member has colorectal cancer diagnosed before age 50 years; **OR**,
- Member has synchronous or metachronous HNPCC-related cancers*, regardless of age; **OR**,
- Member has colorectal cancer with microsatellite instability-high (MSI-H) histology, where cancer is diagnosed before age 60 years; **OR**,
- Colorectal cancer is diagnosed in a member with one or more first-degree relatives with an HNPCC-related cancer*, with one of the cancers diagnosed under age 50 years; **OR**,
- Colorectal cancer is diagnosed in a member with two or more first- or second- degree relatives with an HNPCC-related cancer*, regardless of age.

***Hereditary non-polyposis colorectal cancer (HNPCC)-related cancers include:**

- **153.0 – 154.8** Colorectal
- **182.0** Endometrial
- **151.0 – 181.8** Gastric
- **183.0** Ovarian
- **157.0 – 157.8** Pancreas
- **189.1 – 189.2** Ureter and renal pelvis
- **191.0 – 191.8** Brain (usually glioblastoma as seen in Turcot syndrome)
- **152.0 – 152.8** Small intestinal cancers
- **216.0 – 216.8** Sebaceous gland adenomas in Muir-Torre syndrome
- **238.2** Sebaceous gland keratoacanthomas in Muir-Torre syndrome

CODING

CPT®* Codes

- 83890** Molecular diagnostics; molecular isolation or extraction
- 83891** Molecular diagnostics; isolation or extraction of highly purified nucleic acid
- 83892** Molecular diagnostics; enzymatic digestion
- 83894** Molecular diagnostics; separation by gel electrophoresis (eg, agarose, polyacrylamide)
- 83898** Molecular diagnostics; amplification, target, each nucleic acid sequence
- 83900** Molecular diagnostics; amplification, target, multiplex, first 2 nucleic acid sequences
- 83901+** Molecular diagnostics; amplification, target, multiplex, each additional nucleic acid sequence beyond 2
+List separately in addition to code for primary procedure.
- 83904** Molecular diagnostics; mutation identification by sequencing, single segment, each segment
- 83907** Molecular diagnostics; amplification, target, lysis of cells prior to nucleic acid extraction (eg, stool specimens, paraffin embedded tissue), each specimen.

83909 Molecular diagnostics; separation and identification by high resolution technique (eg, capillary electrophoresis)

83912 Molecular diagnostics; interpretation and report

Genetic Test Name and Applicable CPT ®*Codes

HNPCC, MLH1 Mutation, One Exon	83891, 83892, 83898, 83904, 83909, 83912
HNPCC, MSH2 Mutation, One Exon	83891, 83892, 83898, 83904, 83909, 83912
HNPCC, MSH6 Mutation	83891, 83892, 83898 (x18), 83904 (x18), 83909, 83912
HNPCC, MSH6 Mutation, One Exon	83891, 83892, 83898, 83904, 83909, 83912
HNPCC, Microsatellite Instability (MSI)	83890, 83890(x2), 83900(x2), 83901(x6), 83907, 83909(x2), 83912
HNPCC, MSH2 Gene Sequencing	83891, 83892(x17), 83894, 83898(x17), 83904(x17), 83912
HNPCC, MLH1 Gene Sequencing	83891, 83892(x19), 83894, 83898(x19), 83904(x19), 83912
HNPCC, MLH1 & MSH2 Mutations	83891, 83892(x36), 83894(x2), 83898(x36), 83904(x36), 83912
HNPCC, MLH1 & MSH2 Mutations (Deletion & Duplication)	83891, 83900, 83901(x39), 83909(x2), 83912

ICD-9-CM Procedure Codes - No applicable codes

HCPCS Level II Codes®*

- S3828** Complete gene sequence analysis; MLH1 gene
- S3829** Complete gene sequence analysis; MSH2 gene
- S3830** Complete mlh1 and mlh2 gene sequence analysis for hereditary nonpolyposis colorectal cancer (HNPCC) genetic testing
- S3831** Single-mutation analysis (in individual with a known mlh1 and mlh2 mutation in the family) for hereditary nonpolyposis colorectal cancer (HNPCC) genetic testing
- S3833** Complete APC gene sequence analysis for susceptibility to familial adenomatous polyposis (FAP) and attenuated FAP
- S3834** Single-mutation analysis (in individuals with a known APC mutation in the family) for susceptibility to familial adenomatous polyposis (FAP) and attenuated FAP

Note: S- Codes are NON COVERED FOR MEDICARE – Refer to HCPCS Level II Temporary National Codes

Covered ICD-9-CM Diagnosis Codes

- 153.0 – 153.8** Malignant neoplasm of colon
- 154.0 – 154.8** Malignant neoplasm of rectum, rectosigmoid junction, and anus
- V10.00** Personal history of malignant neoplasm of gastrointestinal tract, unspecified
- V10.05** Personal history of malignant neoplasm of large intestine
- V10.06** Personal history of malignant neoplasm of rectum, rectosigmoid junction, and anus
- V16.0** Family history of malignant neoplasm of gastrointestinal tract

*Current Procedural Terminology (CPT) 2012 American Medical Association: Chicago, IL.©©

REFERENCES

Peer Reviewed

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Government Agencies, Professional and Medical Organizations

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HISTORY AND REVISIONS

Date	Action
2/2/2012	<ul style="list-style-type: none">• Approved by MPC. No changes.
12/1/2011	<ul style="list-style-type: none">• New template design approved by MPC.
2/18/2011	<ul style="list-style-type: none">• Approved by MPC.