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.
GENETIC TESTING FOR FAMILIAL ADENOMATOUS POLYPOSIS AND MYH-ASSOCIATED POLYPOSIS (LYNCH SYNDROME)

HS-160

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. Note: The lines of business (LOB) are subject to change without notice; consult www.wellcare.com/Providers/CCGs for list of current LOBs.

BACKGROUND

Familial Adenomatous Polyposis (FAP) and Attenuated Familial Adenomatous Polyposis (AFAP)

FAP and AFAP are inherited in an autosomal dominant manner. Approximately 75–80% of individuals with these conditions have an affected parent. Offspring of an affected individual have a 50% risk of inheriting the altered APC gene. FAP is characterized by a young onset (age 12–15 years) and the development of multiple (at least 100) adenomatous polyps in the colon and rectum. Additional findings include congenital hypertrophy of retinal pigment epithelium (CHRPE), osteomas, supernumerary teeth, odontomas desmoids, epidermoid cysts, duodenal and other small bowel adenomas, gastric fundic gland polyps. There is also increased risk of medulloblastoma, papillary carcinoma of the thyroid, hepatoblastoma pancreatic and gastric cancers. Considered almost 100% penetrant, adenomas develop in approximately half of all patients with FAP by age 15, and in 95% by age 35. Without intervention, most individuals with FAP will develop colon or rectal cancer by the fourth decade of life. Thus, screening and intervention for at-risk persons is critical and typically begins at puberty.

AFAP, an attenuated variety of FAP, is characterized by a significant risk for colon cancer, but fewer colonic polyps than classic FAP. An average of 30 polyps is seen in AFAP. The polyps tend to be found more proximally in the colon than in classic FAP. The average age of colon cancer diagnosis in individuals with AFAP is age 50–55 years, approximately 10–15 years later than in those with classic FAP, but earlier than that seen in individuals with sporadically occurring colon cancer. Mutations of the APC gene are also associated with AFAP. APC mutation testing is positive in approximately 60% of cases.

Most cases of FAP and AFAP are associated with mutations in the APC gene, a tumor suppressor or gatekeeper gene that controls cell proliferation. More than 300 different disease associated mutations of the APC gene have been identified. Most are insertions, deletions and nonsense mutations that lead to frame shifts or premature stop codons, resulting in truncation of the APC gene product. The penetrance of FAP in terms of colonic adenomatous polyposis and colon cancer is virtually 100% in untreated individuals. APC-associated polyposis conditions have historically accounted for an average of 0.5% of all colorectal cancers; however, this figure is declining as more at-risk family members undergo successful treatment following early polyp detection and prophylactic colectomy (Burt and Solomon, 2005). APC testing does not change clinical management of FAP or AFAP affected individuals but is recommended for familial risk assessment.

MYH-Associated Polyposis (MAP) 1,3,4,5

MYH-Associated Polyposis (MAP), also known as MUTYH-associated polyposis, is a recently described syndrome that is also characterized by adenomatous polyps. It is an autosomal-recessive syndrome. It is estimated that MAP is responsible for 1.4% of all adenomatous polyposis and 20% of adenomatous polyposis without mutation of the APC gene (Lefevre, et al., 2006). MAP is caused by biallelic mutations in the MutY human homolog (MYH) gene. Generally, most individuals with MAP will have less than 100 polyps (approximately 15–100 polyps). The median age of presentation is in the mid-forties to late fifties. The NCCN notes that screening and surveillance for these individuals are based on limited retrospective data, with genetic counseling and testing recommended for siblings of affected patients, as well as for patients with adenomatous polyposis (more than 10 adenomas or more than 15 cumulative adenomas in 10 years) whose family is consistent with recessive inheritance (NCCN, 2008). It is also noted that testing for APC mutation usually precedes testing for MYH mutations, except in families where only
siblings are affected, which suggests recessive inheritance.

From a clinical perspective, there appears to be little doubt that screening for Lynch syndrome is an effective strategy to identify patients who are at high risk and need close surveillance, and to try to avoid further malignancies or new malignancies in their relatives who are also carriers of MMR gene sequence variants. Unfortunately, with currently available technologies, the cost of identifying patients for screening through the Bethesda criteria and the screening process, especially MMR gene analysis, are both time-intensive and costly. Consequently, research has focused on making screening for Lynch syndrome more accurate and cost-effective by defining the patient population that should be screened, and by excluding patients from MMR gene analysis who are more likely to have sporadic CRC rather than Lynch syndrome, through the use of MLH1 methylation or BRAF p.Val600Glu testing.¹

The following professional organizations have endorsed testing for Lynch Syndrome:

*American Gastroenterological Association (AGA)⁶*

The AGA suggests that genetic testing for Lynch syndrome should be offered to first-degree relatives of individuals with a known inherited sequence variant in an MMR gene. Furthermore, genetic testing should also be offered to those without a known familial sequence variant in an MMR gene, but who do match 1 of the first 3 components of the revised Bethesda criteria (note that there is some confusion in this report between the original and revised Bethesda guidelines):

- Individuals with cancer in families that meet the Amsterdam criteria;
- Individuals with 2 HNPCC-related tumors, including synchronous and metachronous CRC or associated extracolonic cancer (endometrium, ovarian, gastric, hepatobiliary, or small bowel cancer, or transitional cell carcinoma of the renal pelvis or ureter);
- Individuals with CRC and a first-degree relative with CRC or HNPCC-related extracolonic cancer or a colorectal adenoma; 1 of the cancers diagnosed at < 45 years of age, and the adenoma diagnosed at < 40 years of age.

The AGA also suggests an alternative approach, which is to perform MSI testing on any patient who meets the revised Bethesda guidelines, followed by genetic testing for the DNA MMR sequence variants in those patients found to be MSI-H.

*American College of Gastroenterology¹*

The revised guidelines indicate the following for Lynch syndrome based on weak evidence from clinical trials:

- Patients who meet the revised Bethesda criteria should undergo MSI and/or IHC testing of their tumor or a family member’s tumor for MMR proteins;
- Patients who test positive can be offered genetic testing to detect MMR gene sequence variants.

Those with positive genetic testing, or at risk when genetic testing is unsuccessful in an affected proband, should undergo colonoscopy every 2 years beginning at 20 to 25 years of age, until 40 years of age, then annually.

*National Comprehensive Cancer Network (NCCN)²*

The NCCN guidelines include a flowchart for CRC screening for Lynch syndrome, which is described below. The following are risk factors for Lynch syndrome in the extended family pedigree:

- Autosomal dominant inheritance pattern;
• Colon cancer or other Lynch syndrome–related cancers in first- or second-degree family member;
• Colon cancer at < 50 years of age;
• Endometrial cancer at < 50 years of age;
• Multiple primaries, including colorectal, endometrial, ovarian, duodenal/small bowel, gastric, ureteral/renal pelvis, sebaceous adenomas or carcinomas, hepatobiliary/pancreas, brain tumors (particularly glioblastomas);
• Right-sided colon cancer predominance and/or MSI histology.

More information regarding outcomes following a risk assessment, consult the NCCN guideline.

The NCCN recommends that genetic testing for individuals in whom a familial sequence variant is not known should initially focus on the MSH2 and MLH1 genes, followed by testing of the MSH6 and PMS2 genes if no sequence variant is found.2

Society of Gynecologic Oncologists7,8,9

The Society of Gynecologic Oncologists has published a statement on risk assessment for inherited gynecological cancer. These recommendations, which were developed with the aid of an unrestricted educational grant from Myriad Genetics (a company involved in genetic testing for a variety of disorders, including colorectal and breast cancers), indicate the following:

Genetic risk assessment should be performed for patients who have > 20% to 25% risk of having an inherited predisposition to endometrial, colorectal, and related cancers. Such patients are defined by the following criteria:

• Patients with CRC or endometrial cancer who meet the revised Amsterdam criteria as listed below11:
  o At least 3 relatives with a Lynch syndrome–associated cancer (CRC, cancer of the endometrium, small bowel, ureter, or renal pelvis) in 1 lineage;
  o 1 affected individual should be a first-degree relative of the other 2;
  o At least 2 successive generations should be affected;
  o At least 1 Lynch syndrome–associated cancer should be diagnosed before age 50.

• Patients with synchronous or metachronous CRC or endometrial cancer, with the first cancer diagnosed prior to age 50.
• Patients with synchronous or metachronous ovarian cancer or CRC, with the first cancer diagnosed prior to age 50.
• Patients with CRC or endometrial cancer with evidence of a MMR defect (i.e., MSI or IHC loss of expression of MLH1, MSH2, MSH6, or PMS2).

Patients with a first- or second-degree relative with a known MMR gene mutation. Genetic risk assessment may be offered for patients who have > 5% to 10% risk of having an inherited predisposition to endometrial, colorectal, and related cancers. Such patients are defined by the following criteria:

• Patients with CRC or endometrial cancer diagnosed prior to age 50;
• Patient with endometrial or ovarian cancer with a synchronous or metachronous colon or other Lynch syndrome–associated tumor* at any age;
• Patients with CRC or endometrial cancer and a first-degree relative with a Lynch syndrome–associated tumor* diagnosed prior to age 50;
• Patients with CRC or endometrial cancer diagnosed at any age, with ≥ 2 first- or second-degree relatives with Lynch syndrome–associated tumors*, regardless of age;
• Patients with a first- or second-degree relative who meet the above criteria.

* Lynch syndrome–related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain
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(usually glioblastoma as seen in Turcot syndrome) tumors, sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel.

POSITION STATEMENT

Applicable To:
☑ Medicaid – Hawaii, Kentucky*
☑ Medicare – Easy Choice Health Plan, Hawaii, Kentucky*

For markets noted below, please refer to Care Core National Lab Management criteria (program effective August 2014) available at www.wellcare.com/provider/CCGs.

☑ Medicaid – Florida, Georgia, Illinois, Missouri, New Jersey, New York, South Carolina
☑ Medicare – Arizona, Connecticut, Florida, Georgia, Illinois, Louisiana, Missouri, New Jersey, New York, Ohio, Texas, Windsor

* Kentucky (Medicaid and Medicare) pending state approval; CCG to be used until Care Core is effective in late 2014.

Genetic testing for familial adenomatous polyposis (FAP) or attenuated familial adenomatous polyposis (AFAP) is considered medically necessary if ANY the following criteria are met:

- Members with greater than 20 adenomatous colonic polyps (211.3) during their lifetime; OR,
- Member has a first or second degree relative diagnosed with FAP or AFAP (V18.51); OR,
- Member has a first or second degree relative with a known FAP or AFAP gene mutation (APC gene).

Genetic testing for MYH-associated polyposis (MAP) is considered medically necessary if EITHER of the following criteria are met:

- Member with greater than 10 adenomatous colonic polyps (211.3) (or greater than 15 cumulative adenomas in 10 years V12.72); AND,
  - Have a recessive inheritance (family history positive only for siblings); OR,
  - Member has a negative result on a APC mutation test (FAP or AFAP gene mutation test)
- OR;
- Member is an asymptomatic sibling of an individual with known MYH-associated polyposis (V18.51).

CODING

CPT® Codes

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<th>Code</th>
<th>Description</th>
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<tr>
<td>81201</td>
<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence</td>
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<td>81202</td>
<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants</td>
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<tr>
<td>81203</td>
<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants</td>
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<td>BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in BRCA1 (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)</td>
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<td>81213</td>
<td>BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis;</td>
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uncommon duplication/deletion variants [BART]

81214  
**BRCA1** (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 8121404 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)

81215  
**BRCA1** (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant

81216  
**BRCA2** (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis

81217  
**BRCA2** (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant

81292  
**MLH1** (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

81293  
**MLH1** (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants

81294  
**MLH1** (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

81295  
**MSH2** (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

81296  
**MSH2** (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants

81297  
**MSH2** (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

81298  
**MSH6** (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

81299  
**MSH6** (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants

81300  
**MSH6** (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

81301  
Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed

81317  
**PMS2** (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

81318  
**PMS2** (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants

81319  
**PMS2** (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

81401  
Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) [when specified as the following]:

**MUTYH** (mutY homolog [E.coli]) (eg, MYH-associated polyposis), common variants (eg, Y165C, G382D)

81406  
Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) [when specified as the following]:

**MUTYH** (mutY homolog [E.coli]) (eg, MYH-associated polyposis), full gene sequence

ICD-9-CM Procedure Codes - No Applicable Codes

HCPCS ®*  Level II Codes

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  
*S- Codes are NON COVERED FOR MEDICARE – Refer to HCPCS Level II Temporary National Codes
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Covered ICD-9-CM Diagnosis Codes
153 Malignant neoplasm of the colon
154.0 Malignant neoplasm of the rectosigmoid junction
197.5 Secondary malignant neoplasm of the large intestine and rectum
211.3 Benign neoplasm of the colon
211.3 Colonic Polyps
211.4 Benign neoplasm of the rectum and anal canal
230.3 Carcinoma in situ of the colon
230.4 Carcinoma in situ to the rectosigmoid junction
235.2 Neoplasm of uncertain behavior of digestive system; intestine and rectum
239 Neoplasm of unspecified nature; digestive system
V10.05 Personal history of malignant neoplasm; large intestine
V10.06 Personal history of malignant neoplasm; rectosigmoid junction
V12.72 Personal history of Colonic Polyps
V16.0 Family history of malignant neoplasm; gastrointestinal tract
V18.51 Family history of Colonic Polyps
V76.41 Special screening for malignant neoplasm; rectum

Covered ICD-10-CM Diagnosis Codes
C18.0-C18.9 Malignant neoplasm of colon
C19 Malignant neoplasm of rectosigmoid junction
C78.5 Secondary malignant neoplasm of large intestine and rectum
D01.0-D01.3 Carcinoma in situ of other and unspecified digestive organs
D12.0-D12.9 Benign neoplasm of colon, rectum, anus and anal canal
D12.2 - D12.6 Benign neoplasm of colon
D37.2 Neoplasm of uncertain behavior of small intestine
D37.4 Neoplasm of uncertain behavior of colon
D37.5 Neoplasm of uncertain behavior of rectum
D49.0 Neoplasm of unspecified behavior of digestive system
Z12.10-Z12.13 Encounter for screening for malignant neoplasm of intestinal tract
Z80.0 Family history of malignant neoplasm of digestive organs
Z83.71 Family history of colonic polyps
Z85.030-Z85.038 Personal history of other malignant neoplasm of large intestine
Z85.040-Z85.048 Personal history of other malignant neoplasm of rectum, rectosigmoid junction, and anus
Z86.010 Personal history of colonic polyps


REFERENCES


**MEDICAL POLICY COMMITTEE HISTORY AND REVISIONS**

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