

Genetic Testing for Colorectal Cancer/Lynch Syndrome

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Definitions

<p>Lynch Syndrome (LS) (aka Hereditary nonpolyposis colorectal cancer [HNPCC])</p>	<p>An autosomal dominant condition caused by mutations in the EPCAM gene or one of several DNA mismatch repair genes (MSH2 and MLH1 predominantly; MSH6 to a lesser extent) and accounts for 3-5% of all colorectal cancers. In addition to a predominantly right-sided and early onset colorectal cancer, individuals with HNPCC have an increased risk of extracolonic cancers, most commonly endometrial. Other associated cancers include ovarian, stomach, small bowel, pancreatic, hepatobiliary, brain (usually glioblastoma as seen in Turcot Syndrome), ureteral and renal pelvis. Sebaceous gland adenomas and keratoacanthomas are seen in Muir-Torre Syndrome (a rare subtype of HNPCC). (Unlike familial adenomatous polyposis, individuals with HNPCC do not have an unusual number of colonic polyps).</p> <p>The Amsterdam and Bethesda criteria, sometimes used interchangeably, were created to serve different purposes:</p> <ol style="list-style-type: none"> 1. Amsterdam — used to identify individuals who meet the definition of HNPCC. 2. Bethesda — intended to help identify tumors that should be tested for microsatellite instability, thereby identifying individuals at risk for HNPCC. If microsatellite instability is high, then more specific gene testing is appropriate (MLH1, MSH2, MSH6, PMS2).
<p>Familial adenomatous polyposis (FAP) (aka Gardner syndrome, familial polyposis coli or adenomatous polyposis coli [APC])</p>	<p>An autosomal dominant condition caused by mutations of the Adenomatous Polyposis Coli (APC) gene and accounts for less than 1% of all colorectal cancers. Individuals with FAP have multiple (>100) precancerous polyps in the colon and rectum developing after the first decade of life and may also have polyps in the upper GI tract, dental abnormalities (especially supernumerary teeth and/or odontomas) and extraintestinal manifestations such as osteomas and epidermoid cysts and fibromas, desmoid tumors, congenital hypertrophy of retinal pigment epithelium (CHRPE) and other malignant changes such as papillary thyroid cancer, gastric and pancreatic cancers, hepatoblastoma and medulloblastoma. FAP may be associated with central nervous system (CNS) tumors, referred to as Turcot syndrome.</p>
<p>Attenuated FAP</p>	<p>A subset of FAP; affected individuals have a later disease onset with fewer than 100 adenomatous polyps in the colorectum. The incidence is unknown but may be similar to FAP. Testing of the APC gene also plays a role in the evaluation of individuals with suspected attenuated FAP. Upper GI findings and papillary thyroid cancer risk is similar to classic FAP. Other extraintestinal manifestation including CHRPE and desmoids are rare.</p>

MYH-associated neoplasia (aka MYH polyposis or MYH-associated polyposis [MAP])	An autosomal recessive condition resulting from defects in the Mut Y homolog (MYH) genes. Individuals have multiple colorectal adenomas with or without cancer. This condition may account for a portion of individuals that present with multiple adenomas like FAP but are negative for APC gene mutations.
Serrated polyposis syndrome (previously termed hyperplastic polyposis)	Comprising multiple colorectal serrated polyps (hyperplastic polyps, sessile serrated adenomas/polyps and traditional serrated adenomas). Whether condition is inherited or acquired is uncertain. Serrated polyps typically predominate with affected individuals presenting with multiple colorectal adenomas. Individuals with serrated polyposis may also have a family history of colorectal cancer, although it is uncommon for more than one family-member to meet the syndrome's diagnostic criteria.
Hamartomatous polyp syndromes	Hamartomatous syndrome conditions (e.g. Juvenile polyposis syndrome [JPS] caused by SMADA4 and BMPR1A mutations; Peutz-Jeghers syndrome [PJS] caused by STK11 mutations and PTEN hamartomatous syndromes) — associated with increased risk for hamartomatous polyps and colon cancer that is usually distinguished by extracolonic manifestations as well as hamartomatous rather than adenomatous pathology.

Applicable testing

Microsatellite instability (MSI), LS/HNPCC (MLH1, MSH2, MSH6, PMS2, EPCAM), FAP coli and attenuated FAP coli (APC genetic testing), MYH-associated neoplasia or MAP (MYH genetic testing).

Related Medical Guidelines

[Genetic Testing for PTEN Hamartoma Tumor Syndrome](#)

[MYvantage® Hereditary Comprehensive Cancer Panel](#)

Guideline

1. **Lynch Syndrome (LS)/HNPCC** — EPCAM, MLH1, MSH2, MSH6, and PMS2 gene and gene panel testing may be indicated when **one** of the following (a or b) is applicable:

Diagnosis or screening, as indicated by 1 or more of the following:

- a. EPCAM, MLH1, MSH2, MSH6, or PMS2 gene or limited gene panel (i.e., EPCAM, MLH1, MSH2, MSH6, PMS2 genes) testing when **personal history** increases risk, as indicated by 1 or more of the following:
 - i. Personal history of colorectal cancer diagnosed before age 50 years
 - ii. Personal history of colorectal cancer and 1 or more additional positively diagnosed tumors associated with Lynch syndrome[A] regardless of age
 - iii. Personal history of colorectal or endometrial cancer, and one or more first-degree[B] or second-degree[C] relatives with Lynch syndrome-related cancer diagnosed before age 50 years
 - iv. Personal history of colorectal or endometrial cancer, and 2 or more first-degree[B] or second-degree[C] relatives with Lynch syndrome-related cancers, regardless of age
 - v. Personal history of colorectal cancer or endometrial cancer with high microsatellite instability or pathologic immunohistochemistry on cancer tissue testing[D]
 - vi. Personal history of endometrial cancer diagnosed before age 50 years
 - vii. Personal history of synchronous (simultaneous) or metachronous (diagnosed at different times) colorectal cancer or Lynch syndrome-related tumors[A] regardless of age
 - viii. Member with a LS-related cancer [A] or unaffected member with a ≥5% risk of having an MMR gene mutation based on predictive models (PREMM5, MMRpro, MMRpredict)
- b. EPCAM, MLH1, MSH2, MSH6, or PMS2 gene testing when **family history** increases risk, as indicated by 1 or more of the following:

- i. First-degree relative[B] of person with known EPCAM, MLH1, MSH2, MSH6, or PMS2 gene mutation by DNA sequence testing
- ii. One or more first-degree relatives[B] diagnosed with colorectal cancer or Lynch syndrome-related tumor[A] before age 50 years
- iii. One or more first-degree relatives[B] with colorectal or endometrial cancer, and another synchronous or metachronous Lynch syndrome-related cancer
- iv. Two or more first-degree[B] or second-degree[C] relatives diagnosed with colorectal cancer or Lynch syndrome-related tumor,[A] with at least 1 diagnosed before age 50 years
- v. Three or more first-degree[B] or second-degree[C] relatives with Lynch syndrome-related cancers, regardless of age

Footnotes

[A] Lynch syndrome-related tumors include colorectal, endometrial, stomach, small bowel, ovarian, pancreas, prostate, ureter and renal pelvis, biliary tract, brain/CNS, and skin (eg, sebaceous gland adenomas, keratoacanthomas) tumors

[B] First-degree relatives consist of male or female parents, siblings, or children

[C] Second-degree relatives consist of male or female grandparents, grandchildren, aunts, uncles, nieces, nephews, or half-siblings.

[D] Loss of protein expression of the MLH1 gene on immunohistochemistry and subsequent positive BRAF mutation virtually excludes Lynch syndrome and obviates the need for germline mismatch repair gene testing; the added step of BRAF mutation testing is thought to avoid nearly half of mismatch repair gene mutation testing. Histology that is suggestive of the need to perform microsatellite instability testing includes tumor-infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous or signet ring differentiation, or medullary growth pattern

2. Familial adenomatous polyposis (FAP) coli or attenuated FAP; 1 of the following:

- a. Member has > 10 colorectal adenomatous polyps
- b. Member has a 1st degree relative(s) with a known APC mutation
- c. The individual has a personal history of a desmoid tumor

Note: APC negative members should be tested for MUTYH. Members with Serrated Polyposis Syndrome with associated adenomas should also be tested for MUTYH.

Limitations/Exclusions

1. General population screening
2. For detection of APC1307K, an APC missense mutation of unclear clinical significance found in Ashkenazi Jewish population

Revision History

4/12/2019 — updated commensurate with National Cancer Care Network (NCCN).

3/11/2016 — added indication to Lynch Syndrome Section for endometrial cancer.

Applicable Procedure Codes

81201	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
81202	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
81203	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants
81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
81288	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
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
81435	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11
81436	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); duplication/deletion analysis panel, must include analysis of at least 5 genes, including MLH1, MSH2, EPCAM, SMAD4, and STK11

Applicable ICD-10 Diagnosis Codes

C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of colon
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.0	Malignant neoplasm of anus, unspecified
C21.1	Malignant neoplasm of anal canal
C21.2	Malignant neoplasm of cloacogenic zone
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
D01.0	Carcinoma in situ of colon
D01.40	Carcinoma in situ of unspecified part of intestine
D01.49	Carcinoma in situ of other parts of intestine
Z15.09	Genetic susceptibility to other malignant neoplasm
Z80.0	Family history of malignant neoplasm of digestive organs
Z83.71	Family history of colonic polyps
Z85.00	Personal history of malignant neoplasm of unspecified digestive organ
Z85.028	Personal history of other malignant neoplasm of stomach
Z85.038	Personal history of other malignant neoplasm of large intestine
Z85.048	Personal history of other malignant neoplasm of rectum, rectosigmoid junction, and anus
Z85.068	Personal history of other malignant neoplasm of small intestine
Z85.07	Personal history of malignant neoplasm of pancreas
Z85.09	Personal history of malignant neoplasm of other digestive organs
Z85.42	Personal history of malignant neoplasm of other parts of uterus
Z85.43	Personal history of malignant neoplasm of ovary
Z85.46	Personal history of malignant neoplasm of prostate
Z85.51	Personal history of malignant neoplasm of bladder
Z85.54	Personal history of malignant neoplasm of ureter
Z86.010	Personal history of colonic polyps

References

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