MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**Germline Genetic Testing for Hereditary Cancers**
Policy Number	**2.02.60**
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Product Disclaimer	• *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan or Child Health Plus product), medical policy criteria apply to the benefit.* • *If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.* • *If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.* • *If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.*

POLICY STATEMENT

I. Based upon our criteria and assessment of the peer-reviewed literature, including the National Comprehensive Cancer Network (NCCN) clinical guidelines, genetic testing for hereditary cancer is considered **medically appropriate** in the following circumstances:
   A. Individuals with any blood relative with a known pathogenic or likely pathogenic variant in a cancer susceptibility gene. Testing for the specific known pathogenic or likely pathogenic variant is appropriate.
   B. Individuals meeting the criteria below but who tested negative with previous limited testing (e.g., single gene and/or absent deletion duplication analysis) and are interested in pursuing multigene testing
   C. A pathogenic or likely pathogenic variant identified on tumor genomic (somatic) testing that has clinical implications if also identified in the germline
   D. To aid in systemic therapy and surgical decision making, including when treatment with poly adenosine diphosphate-ribose polymerase (PARP) inhibitors is being considered for the treatment of metastatic breast cancer, advanced ovarian cancer, exocrine pancreatic cancer, or metastatic castration-resistant prostate cancer.
   E. Testing of unaffected (an individual who does not have cancer) family members should only be considered when all appropriate affected family members are unavailable for testing and must have well documented reasons for unavailability AND the unaffected family member with the highest probability of mutation (closest blood relative) should the one tested.
   F. Individuals with limited family history (e.g., fewer than two first- or second-degree female relatives on the same side of the family or female relatives surviving beyond 45 years of age in either lineage; or, if adopted, no birth family history is known).
   G. The individual is the most appropriate person to be tested according to Policy Statement I.E **AND** meets criteria for specific genetic testing for susceptibility to:
      1. Breast cancer, refer to Policy Statement VI.A; or
      2. Ovarian cancer, refer to Policy Statement VI.B; or

3. Pancreatic cancer, refer to Policy Statement VI.C; or
4. Prostate cancer, refer to Policy Statement VI.D; or
5. Colorectal cancer syndromes, refer to Policy Statement VI.E; or
6. Cowden syndrome, refer to Policy Statement VI.F; or
7. Li Fraumeni Syndrome, refer to Policy Statement VI.G; or
8. Hereditary diffuse gastric cancer syndrome, refer to Policy Statement VI.H; or
9. Familial medullary thyroid carcinoma, refer to Policy Statement VI.I.

II. Based upon our criteria and assessment of the peer-reviewed literature, including the NCCN clinical guidelines, genetic testing by next generation sequencing multi-gene panels (e.g., CancerNext, OncoGene Dx, and myRisk Hereditary Cancer panel) is considered **medically appropriate** when an individual meets criteria in Policy Statement I (except Policy Statement I.A, I.D and I.G.9).

III. Based upon our criteria and assessment of the peer-reviewed literature, genetic testing for hereditary cancer is considered **not medically necessary** for the following indications:
- A. Genetic screening of unaffected members of a family with a known absence of genetic pathogenic variants in the family (e.g., the affected individuals at high risk of mutation in the family have been tested and are negative).
- B. Genetic screening of unaffected minors less than 18 years of age.
- C. Testing with a multigene panel when there is a known pathogenic variant in a first or second degree relative.
- D. Genetic screening for genetic pathogenic variants in general population with no family history.
- E. Genetic screening for genetic pathogenic variants when performed primarily for the medical management of other family members not covered by the affected member's subscriber agreement.
- F. Genetic testing for individuals meeting criteria in Policy Statement I but who tested negative with previous testing is considered a duplicative service (except in the instance of Policy Statement I.B).
- G. Direct-to-consumer testing (e.g., 23 and Me) as these tests have not been validated for clinical use and are not able to provide information that is appropriate for medical management, as these services are not subject to quality-control process, and recent research suggests that the error rate is substantial.
- H. If the genetic test is being done for knowledge only and will not alter management or treatment of the patient.
- I. If there is a high clinical likelihood that the patient has a specific disease, and the screening or treatment will not be modified based on the genetic testing.

IV. Based upon our criteria and assessment of the peer-reviewed literature, genetic testing for variants in other genes associated with hereditary cancer that are part of next-generation sequencing panels (e.g., CancerNext, OncoGene Dx, and/or myRisk testing) in a setting other than the above, is considered **not medically necessary** unless criteria in Policy Statement I are met.

V. Based upon our criteria and assessment of the peer-reviewed literature, including the NCCN clinical guidelines, testing for a variant of unknown significance discovered in a family member, is considered **investigational**.

VI. Based upon our criteria and assessment of the peer-reviewed literature, including the NCCN clinical guidelines, genetic testing for hereditary cancer is considered **medically appropriate** in the following circumstances:

A. **Testing criteria for breast cancer susceptibility genes** (Specifically BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11, and TP53)

1. An individual with a *personal history* of breast cancer with **ANY** of the following specific features:
a. Diagnosed at age 50 years or younger; **OR**
b. Diagnosed at **any age** with **ONE** of the following:
i. To aid in systemic treatment decisions using PARP inhibitors for metastatic breast cancer; **OR**
ii. To aid in adjuvant treatment decisions with Olaparib for high-risk, HER2-negative breast cancer; **OR**

iii.	Triple negative breast cancer (ER-/PR-/HER2-); **OR**
iv.	Multiple primary breast cancers (synchronous or metachronous) ; **OR**
v.	Lobular breast cancer with personal or family history of diffuse gastric cancer (see Policy Statement II.H) ; **OR**
vi.	Male breast cancer; **OR**
vii.	Ashkenazi Jewish ancestry; **OR**
viii.	**One or more** first-, second-, or third-degree relative on the same side of the family with **ANY** of the following: 1. Breast cancer diagnosed at age 50 years or younger; **OR** 2. Male breast cancer; **OR** 3. Ovarian cancer; **OR** 4. Pancreatic cancer; **OR** 5. Prostate cancer with metastatic prostate cancer, **OR** high-risk group prostate cancer, **OR** very high-risk group prostate cancer; **OR**
ix.	**Three or more** first-, second-, or third-degree relatives diagnosed with breast and/or prostate cancer (any grade) on the same side of the family, including the affected member with breast cancer.
2.	An individual with a *family history* of cancer (including those with breast cancer not meeting the above criteria) with an affected first- or second- degree relative and are unable to be tested (see policy statement I.E) with **ANY** of the following:
a.	First- or second-degree relative diagnosed with breast cancer at age 50 years or younger; **OR**
b.	First- or second-degree relative diagnosed at any age with **ANY** of the following specific features:
i.	Triple negative breast cancer (ER-/PR-/HER2-); **OR**
ii.	Multiple primary breast cancers (synchronous or metachronous) ; **OR**
iii.	Lobular breast cancer with personal or family history of diffuse gastric cancer (see Policy Statement II.H) ; **OR**
iv.	Male breast cancer; **OR**
v.	Ashkenazi Jewish ancestry; **OR**
vi.	**One or more** first-, second-, or third-degree relative on the same side of the family with: 1. Breast cancer diagnosed at age 50 years or younger; **OR** 2. Male breast cancer; **OR** 3. Ovarian cancer; **OR** 4. Pancreatic cancer; **OR** 5. Prostate cancer (metastatic prostate cancer, **OR** high-risk group prostate cancer, **OR** very high-risk group prostate cancer); **OR**
vii.	**Three or more** first-, second-, or third-degree relatives diagnosed with breast and/or prostate cancer (any grade) on the same side of the family, including the affected relative with breast cancer; **OR**
c.	Individuals affected or unaffected with breast cancer who otherwise do not meet the criteria above but have a greater than 5% probability of a BRCA 1/2 pathogenic variant based on prior probability models (e.g., Tyrer-Cuzick, BRCAPro, CanRisk).

B. **Testing criteria for ovarian cancer susceptibility genes** (Specifically ATM, BRCA1, BRCA2, BRIP1, Lynch syndrome genes [MLH1, MSH2, MSH6, EPCAM], PALB2, RAD51C, and RAD51D)

1. An individual with a personal history of epithelial ovarian cancer, including fallopian tube cancer or peritoneal cancer, at any age; **OR**
2. An individual with family history of cancer only (unaffected member) with one of the following: a. One or more first or second degree relative with epithelial ovarian cancer (fallopian tube cancer, or peritoneal cancer) at any age; **OR** b. Individuals with greater than 5% probability of a BRCA 1/2 pathogenic or likely pathogenic variant based on prior probability models (e.g., Tyrer-Cuzick, BRCAPro, CanRisk).

C. **Testing criteria for pancreatic cancer susceptibility genes** (Specifically ATM, BRCA1, BRCA2, CDKN2A, Lynch syndrome genes [MLH1, MSH2, MSH6, EPCAM], PALB2, STK11, and TP53)

1. An individual with a personal history of exocrine pancreatic cancer at any age.
2. An individual with family history of cancer only (unaffected member) with one or more first degree relatives diagnosed with exocrine pancreatic cancer at any age.

D. **Testing criteria for prostate cancer susceptibility genes** (Specifically ATM, BRCA1, BRCA2, CHEK2, and HOXB13z)

1. An individual with a *personal history* of prostate cancer with **ANY** of the following specific features: a. Metastatic prostate cancer proven by biopsy and/or radiographic evidence which includes distant metastasis and regional bed or nodes and is not a biochemical recurrence; **OR** b. High-risk group **OR** very-high-risk group prostate cancer; **OR**
2. An individual with a *personal history* of prostate cancer, who do not meet the specific features listed above, **AND** a *family history* of cancer including: a. **one** or more first-, second-, or third-degree relatives with **ANY** of the following: i. Breast cancer diagnosed at age 50 years or younger; **OR** ii. Triple negative breast cancer (ER-/PR-/HER2-) at any age; **OR** iii. Male breast cancer at any age; **OR** iv. Ovarian cancer at any age; **OR** v. Pancreatic cancer at any age; **OR** vi. Metastatic prostate cancer (proven by biopsy and/or radiographic evidence which includes distant metastasis and regional bed or nodes and is not a biochemical recurrence); or high-risk group prostate cancer, or very high-risk group prostate cancer; **OR** vii. Colorectal or endometrial cancer at age 50 years or younger; **OR**
b. One or more first-degree relative with prostate cancer at age 60 years or younger; **OR**
c. Two or more first-, second-, or third-degree relatives with either breast or prostate cancer (any grade) at any age; **OR**
d. Three or more first- or second-degree relatives with Lynch Syndrome-related cancers (colorectal, endometrial, gastric, ovarian, exocrine pancreas, upper tract urothelial, glioblastoma, biliary tract, and small intestinal cancer) ; **OR**
e. Ashkenazi Jewish ancestry; **OR**
f. Individuals with a known familial pathogenic variant in BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6, PMS2, and/or EPCAM; **OR**
3. Individuals with a *personal history* of prostate cancer **AND** breast cancer.

4. An individual with a *family history* of cancer (including those with prostate cancer not meeting the above criteria) with an affected first-degree relative who meets the above criteria (except relatives meeting criteria only for systemic therapy decision-making) and are unable to be tested (see policy statement I.E).

E. **Testing criteria for Colorectal Syndromes:**

1. **Lynch syndrome (LS) or (hereditary nonpolyposis colorectal cancer, (HNPCC))** (germline pathogenic variants of MlH1, MSH2, MSH6, PMS2, EPCAM)

a. An individual with a known LS pathogenic variant in the family; **OR**

b. An individual with a *personal history* of a LS-related cancer* and **ANY** of the following:
   i. Diagnosed at before 50 years of age; **OR**
   ii. Diagnosed at any age with synchronous or metachronous LS-related cancer*; **OR**
   iii. **One** or more first- or second-degree relatives with an LS-related cancer* diagnosed before 50 years of age; **OR**
   iv. **Two** or more first- or second-degree relatives with an LS-related cancer* at **ANY** age; **OR**

c. An individual with a *family history* of **ANY** of the following:
   i. **One** or more first-degree relatives diagnosed with a colorectal or endometrial cancer before 50 years of age**; OR**
   ii. **One** or more first-degree relatives diagnosed with a colorectal or endometrial cancer and a synchronous or metachronous LS-related cancer* at **ANY** age; **OR**
   iii. **Two** or more first- or second-degree relatives with LS-related cancers* with one or more affected relatives diagnosed before 50 years of age; **OR**
   iv. **Three** or more first- or second-degree relatives with LS-related cancers* diagnosed at **ANY** age; **OR**

d. Individuals with a 5% or greater risk of having an MMR gene pathogenic variant based on predictive models (i.e., PREMM5, MMRpro, MMRpredict) ; **OR**

e. Individuals with a personal history of a tumor with MMR deficiency determined by PCR, NGS, or IHC diagnosed at **ANY** age.

*LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreatic, urothelial, brain (usually glioblastoma), biliary tract, and small intestine, as well as sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas as seen in Muir-Torre syndrome.

2. **Microsatellite instability (MSI) testing and Immunohistochemical (IHC) analysis of tumor tissue for expression of one of the four mismatch repair (MMR) genes** is a screening option. MSI testing and IHC analysis may also provide some additional information when Lynch syndrome testing is inconclusive.

a. Tumor tissue of patients with colon or endometrial cancer diagnosed at any age;

b. Tumor screening for MMR deficiency for **ANY** of the following indications when diagnosed at any age:
   i. Sebaceous neoplasms;
   ii. Small bowel adenocarcinoma;
   iii. Ovarian adenocarcinoma;
   iv. Gastric adenocarcinoma;
   v. Pancreatic adenocarcinoma;
   vi. Biliary tract adenocarcinoma;
   vii. Brain adenocarcinoma;
   viii. Bladder/urothelial adenocarcinoma; or
   ix. Adrenocortical cancers.

c. Absent MLH1 expression by IHC should be followed by tumor testing for the presence of BRAF V600E pathogenic variant (or with IHC for BRAF) or for hypermethylation. Those with a germline pathogenic variant are identified as LS patients.

d. Tumor tissue of patients with multiple colon polyps, at least one of which is an adenomatous polyp, and who meet **ANY** of the following criteria:

i. Individuals diagnosed with colorectal cancer before age 50 years;
ii. Presence of synchronous (two or more primary cancers detected simultaneously either preoperatively or in the resected specimen or within three to six months of each other), and metachronous (two or more primary cancers detected after an intervening interval, usually after six months) colorectal Lynch syndrome-associated tumors*, regardless of age;
iii. Individuals with a colorectal tumor with the MSI-H histology (i.e., presence of tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet ring differentiation, or medullary growth pattern);
iv. Individuals with colorectal cancer and one or more first-degree relatives with colorectal cancer and/or Lynch syndrome-related cancer*, with one of the cancers diagnosed before age 50 years;
v. Individuals with colorectal cancer and colorectal cancer diagnosed in two or more first- or second-degree relatives with Lynch syndrome-related tumors*, regardless of age.

*LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastoma, as seen in Turcot syndrome), and small intestinal cancers, as well as sebaceous gland adenomas and keratoacanthomas (as seen in Muir-Torre syndrome).

3. **Adenomatous polyposis coli gene (APC) for familial adenomatous polyposis (FAP) or attenuated familial adenomatous polyposis (AFAP)**

a. Individuals with a *personal history* of 20 or more cumulative adenoma; **OR**

b. Individuals with a known APC pathogenic variant in the family.
(Testing for the specific known familial pathogenic variant rather than full gene sequencing is recommended.); **OR**

c. Individuals with multifocal/bilateral congenital hypertrophy of retinal pigment epithelium (CHRPE) ; **OR**

d. Individuals with *personal history* of **one** or more of the following:
i. between 10 to 19 cumulative adenomas;
ii. desmoid tumor;
iii. hepatoblastoma;
iv. cribriform-morular variant of papillary thyroid cancer;
v. unilateral CHRPE
vi. Five or more lesions/polyps proximal to the rectum that are five mm in size with two or more of these lesions/polyps 10 mm or greater with at least some adenomas; or
vii. More than 20 polyps of any size but distributed throughout the colon with five or more being proximal to the rectum with at least some adenomas.

4. **MUTYH- associated polyposis (MAP)**

a. Individuals with a *personal history* of 20 or more cumulative adenomas; **OR**

b. Individuals with a *personal history* of:

i. 10 or greater adenomas;
ii. Five or more lesions/polyps proximal to the rectum that are five mm in size with two or more of these lesions/polyps 10 mm or greater; or
iii. More than 20 polyps of any size but distributed throughout the colon with five or more being proximal to the rectum; **OR**

c. Individuals with a *family history* including **one** or more siblings with known MUTYH-associated polyposis; **OR**

d. Individuals with a known deleterious MUYTH pathogenic variant in the family.
(Testing for the specific known familial pathogenic variant rather than full gene sequencing is recommended.)

5. **Peutz-Jeghers Syndrome (PJS)** (germline pathogenic variant of STK11)

a. Individuals with *personal history* of **two** or more of the following:
   i. Two or more Peutz-Jeghers-type hamartomatous polyps of the GI tract; and/or
   ii. Mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers; and/or
   iii. Family history of Peutz-Jeghers Syndrome

6. **Juvenile polyposis syndrome (JPS)** (germline pathogenic variants of BMPR1A and/or SMAD4)

a. Individuals with a *personal* history of **one** or more of the following:
   i. Five or more juvenile polyps of the colon;
   ii. Multiple juvenile polyps found throughout the GI tract; or
   iii. Any number of juvenile polyps, in an individual with a family history of JPS; **OR**

b. In first-degree relatives (e.g., siblings, parents, offspring) of patients diagnosed with JPS; **OR**

c. Individuals with a known JPS pathogenic variant in the family.
(Testing for the specific known familial pathogenic variant rather than full gene sequencing is recommended.)

In families with a known BMPR1A pathogenic variant, genetic testing should be performed by age 12–15 when surveillance would begin (or sooner if symptoms warrant evaluation).

If there is a known SMAD4 pathogenic variant in the family, genetic testing should be performed within the first 6 months of life.

F. **Testing criteria for Cowden Syndrome (CS)/PTEN Hamartoma Tumor Syndrome (PHTS)** (germline pathogenic variant of PTEN)

a. Individuals with a *family history* of a known PTEN pathogenic or likely pathogenic variant; **OR**
(Testing for the specific known familial mutation rather than full gene sequencing is recommended.)

b. Individuals with a *personal history* of one of the following:
   i. Bannayan-Riley-Ruvalcaba syndrome (BRRS);
   ii. Adult Lhermitte-Duclos disease (cerebellar tumors);
   iii. Autism spectrum disorder **AND** macrocephaly;
   iv. Two or more biopsy-proven trichilemmomas;
   v. Two or more major criteria (one must be macrocephaly);
   vi. Three major criteria, without macrocephaly;
   vii. One major criteria and three or more minor criteria**; **OR**
   viii. Four or more minor criteria.

**If an individual has two or more major criteria, such as breast cancer and non-medullary thyroid cancer, but does not have macrocephaly, one of the major criteria may be included as one of the three minor criteria to meet testing criteria.

c. Individuals with a first-degree relative with a clinical diagnosis of CS/PHTS or BRRS for whom testing has not been performed. The individual must meet the following diagnostic criteria:
   i. Any one major criterion; or

ii. Two minor criteria.

Major Criteria:	**Minor Criteria:**
a. Breast cancer; or b. Endometrial cancer; or c. Follicular thyroid cancer; or d. Multiple gastrointestinal (GI) hamartomas or ganglioneuromas; or e. Macrocephaly (megalocephaly, i.e., 97% or greater, 58 cm in adult women, 60 cm in adult men); or f. Macular pigmentation of glans penis; or g. Mucocutaneous lesions i. One biopsy-proven trichilemmoma ii. Multiple palmoplantar keratosis (palmoplantar keratotic pits/and or acral hyperkeratotic papules) iii. Multifocal or extensive oral mucosal papillomatosis iv. Multiple cutaneous facial papules (often verrucous).	a. Autism spectrum disorder; or b. Colon cancer; or c. Esophageal glycogenic acanthosis (three or more); or d. Lipomas; or e. Intellectual disability (i.e., IQ 75 or less); or f. Papillary or follicular variant of papillary thyroid cancer; or g. Thyroid structural lesions (e.g., adenoma, nodule(s), goiter); or h. Renal cell carcinoma; or i. Single GI hamartoma or ganglioneuroma; or j. Testicular lipomatosis; or k. Vascular anomalies (including multiple intracranial developmental venous anomalies)

G. **Testing criteria for Li-Fraumeni Syndrome (LFS)** (germline mutations of TP53)

a. Individuals with a *family history* of a known TP53 pathogenic or likely pathogenic variant. (Testing for the specific known familial mutation rather than full gene sequencing is recommended.)

b. Individual meeting Classic LFS criteria which includes **ALL** the following:
i. *Personal history* of sarcoma diagnosed before age 45 years; **AND**
ii. One first-degree relative diagnosed with cancer before age 45 years; **AND**
iii. One additional first- or second-degree relative on the same side of the family diagnosed with cancer before age 45 years or diagnosed with a sarcoma at any age.

c. Individual meeting Chompret criteria which includes **ONE** of the following:
i. Individual with a tumor from the LFS tumor spectrum (e.g., soft tissue sarcoma, osteosarcoma, central nervous system (CNS) tumor, breast cancer, and adrenocortical carcinoma) diagnosed before age 46 years; **AND** at least one first- or second-degree relative with a tumor from the LFS tumor spectrum (other than breast cancer, if the proband has breast cancer) diagnosed before age 56 years **OR** with multiple primaries diagnosed at any age; **OR**
ii. Individual with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum with the *initial* cancer diagnosed before age 46 years; **OR**
iii. Individual with adrenocortical carcinoma, or choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype diagnosed at any age, regardless of the family history; **OR**
iv. Individual with breast cancer diagnosed at age 31 years or younger; may be performed simultaneously with BRCA mutation testing or when BRCA1/BRCA2 is negative.

d. Personal history or family history of pediatric hypodiploid acute lymphoblastic leukemia

H. **Testing criteria for Hereditary diffuse gastric cancer (HDGC)** (germline mutations of CDH1)

a.	Family history (may include individual with personal history) of two cases of gastric cancer in first- or second-degree relatives, at least one of which is a confirmed diffuse gastric cancer diagnosed at any age.
b.	Personal history of diffuse gastric cancer diagnosed before age 50 years with or without a family history.
c.	Personal or family (first- or second-degree relative) history of both lobular breast cancer and diffuse gastric cancer, one of which was diagnosed before age 70 years.
d.	Family history of two cases of lobular breast cancer in first- or second-degree relatives before 50 years of age.
e.	A diagnosis of diffuse gastric cancer at any age in individuals of Māori ethnicity, or with a personal or family history of cleft/lip palate.
f.	Personal history of bilateral lobular breast cancer diagnosed before age 70 years.
g.	An individual from a family with a known CDH1 variant. (Testing for the specific known familial pathogenic variant rather than full gene sequencing is recommended.)

I. **Testing criteria for Familial Medullary Thyroid Carcinoma (germline RET mutations)**

a.	Individuals with a *personal* history of apparently sporadic medullary thyroid carcinoma; **OR**
b.	Individuals with a *family history* of a known RET gene mutation; **OR**
c.	Individuals with a *family history* of medullary thyroid carcinoma but not previously evaluated for RET mutations.

Refer to Corporate Medical Policy #2.02.03 Genetic Testing for Inherited Disorders

Refer to Corporate Medical Policy #4.01.03 Prenatal Genetic Testing

*****Note this policy does not address preimplantation genetic testing, please see above*****

POLICY GUIDELINES

I. The Health Plan and its employees adhere to all State and Federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom such genetic test relates. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test or in compliance with applicable law.

II. Genetic testing is appropriate only when performed by a qualified laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and offered in a setting with adequately trained health care professionals who are qualified to provide appropriate pre- and post-test counseling.

III. Genetic testing is contract dependent. Coverage only applies to members with a valid contract; coverage is not provided for family members without a valid contract.

IV. **Supporting documentation required:**

The following factors will be considered when determining the medical appropriateness of a genetic test:

A. Family history (pedigree) which includes first-, second-, and third-degree relatives, identifying family members affected; and
B. Type of cancer, age at diagnosis for each affected (a personal history of) family member and whether the family

member is living or deceased; and

C. Genetic testing results from any other family members. If family member(s) have not been tested (and are more appropriate to be tested first), clear and distinct rationale as to why the family member(s) cannot be tested (i.e., specific reason why testing was declined); and
D. Documentation of discussion between the physician and member addressing the rationale for genetic testing and treatment options for the member, based on test results.

V. A first-degree relative is a blood relative with whom an individual shares approximately 50% of her/his genes (parents, full siblings, and children). A second-degree relative is a blood relative with whom an individual shares approximately 25% of her/his genes (grandparents, grandchildren, aunts, uncles, nephews, nieces, and half-siblings). A third-degree relative is a blood relative with whom an individual shares approximately 12.5% of her/his genes (great-grandparents, great-grandchildren, great-aunts, great-uncles, first cousins, grand-nieces, or grand-nephews.)

VI. Whenever possible, initial genetic testing should be performed for an affected family member who meets clinical diagnostic criteria, as an affected (personal history of cancer) individual has the highest likelihood for a positive test result. Subsequent testing in unaffected family members can then focus on the mutation found in the affected family member. A negative result for an unaffected (an individual who does not have cancer) individual, with a family history only, is considered indeterminate (uninformative) and does not provide the same level of information as when there is a known deleterious mutation in the family. Testing of unaffected family members in the absence of having tested affected family members significantly limits the interpretation of the test results.

VII. Probability models developed to assist with determining the probability that an individual carries a pathogenic variant:

A. Breast Cancer Risk Assessment Tool by the National Cancer Institute (https://bcrisktool.cancer.gov/calculator.html)
B. Carrier Estimation Algorithm (BOADICEA) (http://ccge.medschl.cam.ac.uk/boadicea/)
C. Tyrer-Cuzick risk model, also known as the International Breast Cancer Intervention Study (IBIS) tool (https://ibis-risk-calculator.magview.com)
D. PREMM5 Lynch Syndrome Prediction Model (https://premm.dfci.harvard.edu)
E. MMRpro (https://projects.iq.harvard.edu/bayesmendel/mmrpro)
F. MMRpredict (https://health-atlas.de/models/12)

*Each mutation probability model has its unique attributes determined by the methods, sample size, and population used to create it. Some models use those using logistic regression, while others use Bayesian analysis or empiric data such as the Myriad prevalence tables.

DESCRIPTION

Breast Cancer

The purpose of BRCA1 and BRCA2 testing is to provide information that will guide decisions regarding cancer prevention, surveillance, and treatment options for individuals who test positive. Women who test negative are at the same risk of developing breast or ovarian cancer as the general population, assuming that there is no history on the other side of the family that might be suggestive of a hereditary cancer syndrome and that there are no other risk factors such as atypia. Thus, these women should be managed based on their family history or other risk factors.

Several genetic syndromes with an autosomal dominant pattern of inheritance that feature breast cancer have been identified. Of these, hereditary breast and ovarian cancer (HBOC) and some cases of hereditary, site-specific breast cancer have causative mutations in BRCA genes in common. Families suspected of having HBOC syndrome are characterized by an increased susceptibility to breast cancer occurring at a young age, bilateral breast cancer, male breast cancer, and ovarian cancer at any age. Other cancers, such as prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, and laryngeal cancer, occur more frequently in HBOC families. Hereditary, site-specific breast cancer families are characterized by early-onset breast cancer, with or without male cases, but without ovarian cancer. In this policy, both are referred to collectively as hereditary breast and/or ovarian cancer.

Germline alterations in two genes, BRCA1 and BRCA2, are associated with an increased risk of breast and ovarian cancers; the lifetime risk of breast cancer is 60% to 85%, and the lifetime risk of ovarian cancer is 15% to 40% for women with either of these mutations. Studies are emerging that are associate BRCA mutations with other cancers such as melanoma, prostate, and pancreatic cancer. The prevalence of BRCA mutations is approximately 0.1% to 0.2% in the general population. Prevalence of BRCA mutations may be much higher in certain ethnic groups with characterized founder mutations (e.g., 2% to 3% in the Ashkenazi Jewish population).

Ovarian Cancer

NCCN guidelines state specific patterns of hereditary breast and ovarian cancers have been found to be linked to pathogenic and likely pathogenic variants in the BRCA1/2 genes. Based on strong evidence that genes beyond BRCA1/2, TP53, and PTEN confer markedly increased risk of breast and/or ovarian cancers, NCCN guidelines have been expanded. There are now several pathogenic variants associated with an increased risk for ovarian cancer, including BRCA1, BRCA2, ATM, BRIP1, PALB2, RAD51C, RAD51D, and Lynch syndrome genes. The histology of ovarian cancers in carriers of a pathogenic and likely pathogenic BRCA1/2 variant is more likely to be characterized as serous adenocarcinoma and high grade compared with ovarian cancers in non-carriers, although endometrioid and clear cell ovarian cancers also have been reported in the former population. pathogenic and likely pathogenic variants are also associated with non-mucinous ovarian carcinoma as opposed to mucinous. Mucinous epithelial ovarian carcinomas may be associated with other pathogenic and likely pathogenic variants, such as TP53, which are implicated in LFS (see below). Non-epithelial ovarian carcinomas (e.g., germ cell and sex cord-stromal tumors) are not significantly associated with a BRCA1/2 pathogenic and likely pathogenic variant, though ovarian sex cord tumor with annular tubules is associated with STK11 pathogenic and likely pathogenic variants. Current data show that ovarian low malignant potential tumors (i.e., borderline epithelial ovarian tumors) are also not associated with a BRCA1/2 pathogenic and likely pathogenic variant.

Prostate Cancer

NCCN Prostate Cancer guidelines defines very high-risk prostate cancer as at least one of the following cT3b-cT4, primary Gleason pattern five (5), two (2) or three (3) high-risk features, or greater than four (4) cores with grade group four (4) or five (5). high risk prostate cancer is defined as having no very-high features and has exactly one high risk feature of cT3a or, grade group four (4) or grade group five (5) or prostate specific antigen (PSA) less than 20. Germline BRCA1/2 pathogenic and likely pathogenic variants are associated with increased risk for prostate cancer. Carriers of a pathogenic and likely pathogenic BRCA1 variant have an estimated 7% to 26% cumulative lifetime risk of prostate cancer, while the cumulative lifetime risk is 19% to 61% for carriers of a pathogenic and likely pathogenic BRCA2 variant. There is evidence that advanced or metastatic prostate cancer is associated with carrying a BRCA2 pathogenic and likely pathogenic variant.

Pancreatic Cancer

Recommendations regarding P/LP variants associated with pancreatic cancer, and pancreas screening for individuals harboring such variants, were added to the NCCN Guidelines in the 2020 update. Germline P/LP variants found in pancreatic adenocarcinoma include BRCA1, BRCA2, CDKN2A, MMR genes associated with Lynch syndrome (i.e., MSH2, MLH1, MSH6, PMS2, EPCAM), ATM, PALB2, STK11, and TP53. Given the considerable rate of predisposing pathogenic and likely pathogenic variants in patients with pancreatic cancer, as well as the fact that typical clinical factors (e.g., young age of onset, family history of cancer) are poorly predictive for identifying carriers of a pathogenic and likely pathogenic variant, universal genetic testing for these individuals is warranted. Given the elevated rates of pathogenic and likely pathogenic variants in pancreatic cancer and that pancreatic cancer risk increases when there is a family history, testing of first-degree relatives of patients may be beneficial. However, testing the patient is preferred. Testing of second-degree relatives is generally not recommended but may be considered in select cases. Family history of pancreatic cancer with unknown histology is often presumed to be exocrine. Detecting a germline pathogenic and likely pathogenic variant can potentially aid in treatment decision-making, particularly regarding systemic therapy options.

Colorectal Cancer/ Polyposis Syndromes

Lynch syndrome (LS), also known as hereditary nonpolyposis colorectal cancer (HNPCC), adenomatous polyposis syndromes (e.g., familial adenomatous polyposis (FAP), attenuated familial adenomatous polyposis (AFAP), MUTYH-associated polyposis (MAP)), and hamartomatous polyposis syndromes (e.g., Peutz-Jeghers syndrome (PJS), and juvenile polyposis syndrome (JPS)) are well-defined hereditary colon cancer syndromes for which genetic testing is now available. Although they account only for an estimated 5% to 10% of colorectal cancers, all of these inherited syndromes have a high risk of colon cancer.

The optimal testing strategy for these types of cancers is to define the specific genetic pathogenic variant in an affected family member and offer genetic counseling and testing of the unaffected family members, to determine whether they have inherited the same pathogenic variant. Identification of the at-risk family members helps guide the decision-making about frequency of surveillance procedures and/or prophylactic treatment. If there is no known personal or family history of a known pathogenic variant in a colorectal polyposis or cancer gene, the patient's personal history of 10 or greater adenomatous polyps, two (2) or greater hamartomatous polyps, or five (5) or greater serrated polyps proximal to the rectum should be determined. Individuals meeting these criteria should have a detailed risk assessment and potential genetic evaluation to rule out polyposis syndromes. If a patient has been diagnosed with CRC with no personal history suspicious of a polyposis syndrome, then the patient should be evaluated for lynch syndrome.

Lynch Syndrome (LS) or Hereditary Nonpolyposis Colorectal Cancer (HNPCC):

LS is associated with pathogenic variants in one of four different genes. These genes are known as MLH1, MSH2, MSH6, and PMS2. A fifth gene, known as EPCAM can have a germline pathogenic variant that inactivates MSH2. All of the genes are involved in DNA mismatch repair (MMR) mechanisms. An LS gene carrier has an approximate 80% risk of colon cancer; mean age of onset is 44 years, and the tumors are primarily right sided. LS is estimated to account for 2% to 4% of colorectal cancers and is also associated with an increased risk of extra colonic cancer. Endometrial cancer is the sentinel cancer in women with an LS pathogenic variant; they have an approximate 60% lifetime risk. Other extracolonic cancers in LS include ovarian, gastric, small bowel, biliary, pancreatic, urinary, and sebaceous gland cancers.

Microsatellite instability (MSI) is also a prognostic factor for survival in many cancers, notably for colon cancer although rare in pancreatic adenocarcinoma. Microsatellites are regions of coding and noncoding DNA where short sequences or single nucleotides of DNA are repeated. MSI is caused by a loss of DNA MMR activity. Mutations in germline MMR genes result in a lack of repair of any errors, such as destabilizing errors introduced during DNA replication that shorten or lengthen microsatellites, which then persist in somatic cells. Tumor samples can be assessed for the sizes of microsatellite markers and classified as MSI high (MSI-H), low (MSI-L), and stable (MSS). The NCCN Panel recommends MSI testing and/or MMR testing on available tumor tissue for sebaceous neoplasms as well as the following adenocarcinomas: small bowel, ovarian, gastric, pancreatic, biliary tract, brain, bladder/urothelial, and adrenocortical cancers regardless of age at diagnosis.

MUTYH-Associated Polyposis (MAP):

MAP is an autosomal recessive form of FAP. Pathogenic variants in the MUTYH gene affect the ability of cells to correct mistakes made during DNA replication. Both copies of the gene are mutated in individuals who have MUTYH-associated polyposis. These germline pathogenic variants in MUTYH predispose persons to multiple adenoma or polyposis coli. The phenotype is often undistinguishable from FAP, although the number of adenomas is often lower. Generally, the mean age at diagnosis is 48 to 56 years. The absolute risk of colorectal cancer is not known. Several extracolonic manifestations have been observed, although their incidence is not yet well- established. Similar to FAP, these include duodenal polyposis, duodenal cancer, osteomas, dental cysts, and congenital hypertrophy of the retinal pigment epithelium. Breast cancer and thyroid cancer, as well as cutaneous tumors (pilomatricomas and sebaceous gland tumors) have also been reported.

FAP and Attenuated FAP (AFAP):

Germline alterations in the adenomatous polyposis coli (APC) gene, located on chromosome 5, are inherited in an autosomal-dominant fashion and are responsible for FAP. The diagnosis is based on clinical findings of multiple colorectal adenomatous polyps (often in excess of 100), with onset as early as 10 years of age. An individual who is a

FAP gene carrier has a near 100% lifetime risk of developing colon cancer. FAP accounts for 1% of all colorectal cancer cases and may also be associated with osteomas of the jaw, skull, and limbs; sebaceous cysts; and pigmented spots on the retina, referred to as Gardner's syndrome. Other cancers are also sometimes observed in FAP including duodenal, thyroid, pancreatic, and hepatoblastoma malignancies. Once a diagnosis of FAP is made in a family, intensive surveillance is recommended for all at-risk relatives because of the high probability of carrying an APC gene pathogenic variant. AFAP, an attenuated variety of FAP, is characterized by fewer than 100 adenomatous polyps in the colorectum with proximal predominance and later onset (age 55). The most informative testing strategy requires that an affected family member to be the first tested.

Juvenile Polyposis Syndrome (JPS):

JPS occurs in approximately one in every 100,000 persons. As with the other syndromes, it is inherited in an autosomal-dominant fashion. It is clinically suspected when three to 10 juvenile polyps are found in the colon, or juvenile polyps are found outside the colon. Polyps are found most often in the colon but may occur throughout the GI tract. Malignancy arises from changes in the juvenile polyps. Patients with JPS often have complications from the polyps early in life but have a colon cancer risk approaching 60% over a lifetime. Gastric, small intestinal, and pancreatic cancers also occur. About 50% to 64% of JPS cases occur due to pathogenic variants in the BMPR1A and SMAD4 genes. In families with a known BMPR1A pathogenic variant, genetic testing should be performed by age 12–15 when surveillance would begin (or sooner if symptoms warrant evaluation). If there is a known SMAD4 pathogenic variant in the family, genetic testing should be performed within the first six months of life due to the risk of hereditary hemorrhagic telangiectasia.

Peutz-Jeghers Syndrome (PJS):

The diagnosis of PJS is based on the family history, mucocutaneous macules, PJS-type intestinal polyps, and presence of a disease-causing pathogenic variant in STK11. PJS is an autosomal-dominant condition characterized by the association of gastrointestinal polyposis**,** mucocutaneous pigmentation, and cancer predisposition. Peutz-Jeghers-type hamartomatous polyps are most common in the small intestine (in order of prevalence: in the jejunum, ileum, and duodenum) but can also occur in the stomach, large bowel, and extraintestinal sites including the renal pelvis, bronchus, gall bladder, nasal passages, urinary bladder, and ureters. Gastrointestinal polyps can result in chronic bleeding and anemia; they also cause recurrent obstruction and intussusception, requiring repeated laparotomy and bowel resection. Mucocutaneous hyperpigmentation presents in childhood as dark blue to dark brown macules around the mouth, eyes, and nostrils, in the perianal area, and on the buccal mucosa. Hyperpigmented macules on the fingers are common. The macules may fade in puberty and adulthood. Individuals with PJS are at increased risk for a wide variety of epithelial malignancies (colorectal, gastric, pancreatic, breast, and ovarian cancers).

While MAP, FAP/AFAP, JPS, and PJS can be identified by the appearance of characteristic colon polyps; whereas LS is identified primarily on family history and related clinical criteria. The Amsterdam II Criteria is one such set of clinical criteria. The Revised Bethesda Guidelines provide clinical direction for the use of microsatellite instability (MSI) testing and IHC analysis to screen colon or endometrial cancer tumor slides to help determine whether the individual and family history may be linked to an LS pathogenic variant.

Amsterdam II Criteria	**Revised Bethesda Guidelines**
The Amsterdam II Criteria (revised from the original to include extracolonic LS-associated cancers) include **ALL** of the following: • Three or more relatives with a histologically verified LS-associated cancer (colorectal cancer or cancer of the endometrium, small bowel, ureter, or renal pelvis); **AND** • One of whom is a first-degree relative of the other two; **AND**	The Revised Bethesda Criteria for testing colorectal tumors or endometrial tumors include **ANY** of the following: • Individuals diagnosed with colorectal cancer before age 50 years; **OR** • Presence of synchronous (two or more primary cancers detected simultaneously, either preoperatively or in the resected specimen, or within three to six months of each other) and metachronous (two or more primary cancers detected after an

• HNPCC-associated cancer involving at least two generations; **AND** • Cancer in one or more affected relatives diagnosed before 50 years of age; **AND** • FAP excluded in any cases of colorectal cancer. Modifications allow for small LS families: these families must have two colorectal cancers in first-degree relatives from at least two generations, with at least one individual diagnosed by age 55 years.	intervening interval, usually after six months) colorectal LS-associated tumors* regardless of age; **OR** • Individuals with colorectal cancer with the MSI-H histology who were diagnosed before age 60 years; **OR** • Individuals with colorectal cancer who have one or more first-degree relatives with colorectal cancer and/or LS-related cancer* at least one of which was diagnosed before age 50 years; **OR** • Individuals with colorectal cancer who have two or more first- or second-degree relatives with LS-related tumors*, regardless of age. *LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastoma, as seen in Turcot syndrome), and small intestinal cancers, as well as sebaceous gland adenomas and keratoacanthomas (as seen in Muir-Torre syndrome).

Serum genetic testing for LS is normally performed to detect a pathogenic variant in one of the MMR genes (MLH1, MSH2, MSH6 or PMS2). Approximately a 1% to 3% of LS families are linked to a pathogenic variant in EPCAM. These families may meet the Amsterdam II criteria but test negative for MLH1, MSH2, MSH6 and PMS2.

MSI and IHC analysis are two tests performed on colorectal or endometrial cancer tumor tissue, to identify individuals who may have LS. The sensitivities of MSI and IHC testing are estimated to be 77% to 89% and 83%, respectively, while specificities are estimated to be 90% and 89%, respectively. MSI testing of tumor DNA is divided into MSI-high and MSI-low categories. MSI-high in tumors refers to changes in two or more of the five microsatellite markers in the National Cancer Institute-recommended panel. MSI testing may be performed initially, followed by IHC, or further testing for pathogenic variants in MLH1, MSH2 and MSH6 genes; if the tumor tissue is found to be MSI-high. For tumors that test MSI-low or microsatellite stable tumors, pathogenic variants in MSH6 or PMS2 are less likely but may be still possible. Further testing may depend on the individual risk, based on family history. IHC analysis of tumor tissue refers to staining tumors tissue for protein expression of the four mismatch genes known to be mutated in LS (MLH1, MSH2, MSH6, and PMS2). A normal IHC test implies that all four mismatch repair proteins are normally expressed, and no underlying mismatch repair gene pathogenic variant is present in the related gene. Loss of protein expression in any one of the mismatch repair genes by IHC guides genetic testing or pathogenic variant detection to the gene where the protein expression is not observed. Consequently, IHC analysis is advantageous in that it can predict which gene is most likely mutated and should be tested for first. As there is a 5% to 10% false negative rate for MSI and IHC testing, the tests are not a prerequisite for each screening test for inherited susceptibility to colorectal or endometrial cancer. Family and personal history, as well as, a clinical evaluation, should be utilized in determining which test should be performed initially.

Cowden Syndrome

Cowden syndrome (CS) is an autosomal dominant disorder associated with germline mutations in the PTEN (phosphatase and tensin homolog) tumor suppressor gene. It is considered to be part of the spectrum of PTEN hamartoma tumor syndromes (PHTS) which also includes Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and Proteus-like syndrome (PLS). Additional clinical syndromes related to germline mutations in PTEN include Lermitte-Duclos disease and autism spectrum disorders with macrocephaly, both of which have been associated with Cowden syndrome. Cowden syndrome has been conservatively estimated to occur in one in 200,000, with an estimated penetrance of 80%. CS is associated with multiple hamartomas and/or cancerous lesions in various organs and tissues,

including the skin, mucous membranes, breast, thyroid, endometrium, and brain. Women diagnosed with CS have a high risk of benign fibrocystic breast disease and their lifetime risk of breast cancer has been estimated at 85% with an average age of diagnosis of 38-46 years.

Li Fraumeni Syndrome

Li Fraumeni syndrome (LFS) is a rare hereditary cancer syndrome associated with germline TP53 gene mutations. Germline mutations in the TP53 gene have been observed in over 50% of families meeting the classical definition of LFS. LFS is a highly penetrant cancer syndrome and is characterized by a wide spectrum of neoplasms occurring at a young age. It is associated with soft tissue sarcomas, osteosarcomas (Ewing's sarcoma is less likely in cases of LFS), premenopausal breast cancer, acute leukemia, colon cancer, adrenal cortex tumors, and brain tumors. The "core" LFS tumors are noted to be sarcoma, breast cancer, adrenocortical tumors, and certain brain tumors because they are the more predominant cancers in this syndrome. Individuals with LFS often present with certain cancers in early childhood and have an increased risk of developing multiple cancers in their lifetime.

Hereditary Diffuse Gastric Cancer Syndrome

Hereditary diffuse gastric cancer (HDGC) is an autosomal dominant syndrome characterized by the development of diffuse (signet ring cell) gastric cancer at a young age. Truncating mutations in CDH1, the gene encoding the cell adhesion molecular E-cadherin, are found in 30% to 50% of cases. The lifetime risk for gastric cancer by age 80 years is estimated to be at 67% for men and 83% for women. Average age at diagnosis of gastric cancer is 37 years. Women with CDH1 mutations are at higher risk of developing lobular carcinoma of the breast with a cumulative lifetime risk for breast cancer of 39% to 52%. While most gastric cancers are considered sporadic, it is estimated that 5% to 10% have a familial component and 3% to 5% are associated with an inherited cancer predisposition syndrome. Individuals with Lynch syndrome (LS) have a 1% to 13% risk of developing gastric cancer. Individuals with Juvenile polyposis syndrome (JPS) have a lifetime risk of 21% for developing gastric cancer when involvement of the upper gastrointestinal tract is present. Individuals with Peutz-Jeghers syndrome (PJS) have a 29% risk of developing gastric cancer. Individuals with familial adenomatous polyposis (FAP), in addition to attenuated FAP (AFAP), have a 1% to 2% lifetime risk for gastric cancer. More than 40% of patients with HDGC do not carry CDH1 mutations, suggesting the existence of additional susceptibility genes.

Familial Medullary Thyroid Carcinoma

Thyroid cancer is the most common malignancy of endocrine tissues, although it accounts for only 1.1% of all non-skin cancers detected annually in the United States. Up to 9% of thyroid cancers are medullary carcinoma. Three distinct but related familial cancer syndromes, together, are responsible for about one-fourth of the incidence of medullary carcinoma of the thyroid; the remaining three-fourths of cases are sporadic. From 90 to 95% of the inherited medullary thyroid carcinomas can be attributed to specific RET (rearranged during transfection) point mutations (multiple endocrine neoplasia - MEN 2A, MEN 2B - or familial medullary thyroid cancer - FMTC). All three of the syndromes (MEN 2A, MEN 2B and FMTC) exhibit an autosomal-dominant pattern of inheritance, with nearly complete penetrance. Thus, over their lifetime, more than 95% of individuals who inherit a mutated gene will develop medullary thyroid carcinoma, if the gland is not removed before the disease is diagnosed by clinical symptoms.

Medullary thyroid carcinoma is surgically curable if detected before it has spread to regional lymph nodes. However, lymph node involvement at diagnosis may be found in up to 75% of patients for whom a thyroid nodule is the first sign of disease. Medullary thyroid carcinoma often recurs and/or spreads despite complete thyroidectomy in those with positive lymph nodes. Thus, early detection and intervention in affected families is critical.

Multigene Panel Testing

Next Generation Sequencing has resulted in the availability of multigene testing, which can simultaneously test more than 50 genes for pathogenic variants, often at costs comparable to single-gene testing. These multigene panels can include genes with pathogenic variants that are associated with high risks of cancer and genes that confer moderate and uncertain risks. The multigene panels can be limited to specific cancer types (e.g., breast, ovarian, colon) or can include many cancer types.

RATIONALE

The genotypes to be detected by a genetic test must be shown by scientifically valid methods to be associated with a high positive predictive value of the occurrence of a disease. Analytical sensitivity and specificity of a genetic test must be of such a level that the test results can and will be used in making treatment decisions.

The American Society of Clinical Oncology (ASCO) recommends that genetic testing be considered when:

I. The individual has a personal or family history features suggestive of a genetic cancer susceptibility condition,
II. The test can be adequately interpreted, and
III. The results will aid in diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer.

Information on the risks and benefits of genetic testing must be presented fully and objectively, without coercion to persons contemplating genetic testing.

The National Comprehensive Cancer Network (NCCN) principles of cancer risk assessment and counseling include the decision to offer genetic testing that involves three stages:

I. pre-test counseling done prior to ordering testing;
II. consideration of the most appropriate tests to order; and
III. post-test counseling done when results are disclosed. It is recommended that a genetic counselor, medical geneticist, oncologist, surgeon, oncology nurse, or other health profession with expertise and experience in cancer genetics be involved at each stage whenever possible. Testing should be considered in appropriate high-risk individuals where it is likely to impact the risk management and/or treatment of the tested individuals and/or their at-risk family members.

Breast Cancer

Studies published in peer-reviewed scientific literature indicate that genetic testing for BRCA1 and BRCA2 mutations is appropriate for individuals who have been identified to be at high risk for hereditary breast and ovarian cancers. Several professional organizations (NCCN, US Preventive Services Task Force, American College of Medical Genetics, and ASCO), have issued statements regarding the role of BRCA testing in the management of high-risk individuals.

NCCN guidelines for Breast Cancer recommend assessing for germline BRCA1/2 mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy. They state while Olaparib and talazoparib are FDA indicated in HER2-negative disease, the panel supports use in any breast cancer subtype associated with a germline mutation. There is lower-level evidence for HER2-positive tumors, therefore category 2A for this setting.

The American Society of Breast Surgeons updated its Consensus Guideline on Genetic Testing for Hereditary Breast Cancer (2019). The recommendations state genetic testing should be made available to all patients with a personal history of breast cancer. Recent data support that genetic testing should be offered to each patient with breast cancer (newly diagnosed or with a personal history). If genetic testing is performed, such testing should include BRCA1/BRCA2 and PALB2, with other genes as appropriate for the clinical scenario and family history. For patients with newly diagnosed breast cancer, identification of a mutation may impact local treatment recommendations (surgery and potentially radiation) and systemic therapy. Additionally, family members may subsequently be offered testing and tailored risk reduction strategies. Patients who had genetic testing previously may benefit from updated testing. Every patient being seen by a breast surgeon, who had genetic testing in the past and no pathogenic variant was identified, should be re-evaluated and updated testing considered. A patient who had negative germline BRCA1 and 2 testing, who is from a family with no pathogenic variants, should be considered for additional testing. Genetic testing performed prior to 2014 most likely would not have had PALB2 or other potentially relevant genes included and may not have included testing for large genomic rearrangements in BRCA1 or BRCA2.

Ovarian Cancer

NCCN guidelines for ovarian cancer state patients with ovarian cancer, fallopian tube cancer, or primary peritoneal cancer should have genetic risk evaluation and germline and somatic testing. Family history (primarily patients having two or

more first-degree relatives with ovarian cancer)—including linkage with BRCA1 and BRCA2 genotypes (hereditary breast and ovarian cancer [HBOC] syndrome) or families affected by Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC] syndrome)—is associated with increased risk of ovarian cancer, particularly early-onset disease. In addition to mutations in BRCA1/2 and the genes associated with Lynch syndrome (e.g., MLH1, MSH2, MSH6, PMS2), germline mutations in a variety of other genes have been associated with increased risk of ovarian cancer (e.g., ATM, BRIP1, NBN, PALB2, STK11, RAD51C, RAD51D). Patients with mutations in BRCA1/2 account for only approximately 15% (range, 7%–21%) of those who have ovarian cancer. Studies testing large panels of genes have found that 3% to 8% of patients with ovarian cancer carry mutations in genes other than BRCA1 and BRCA2 known to be associated with ovarian cancer susceptibility.

U.S. Food and Drug Administration (FDA) granted:

- Accelerated approval to Lynparza (Olaparib), a new drug treatment for women with advanced ovarian cancer associated with defective BRCA genes, as detected by an FDA-approved test.
    - Lynparza is a poly ADP-ribose polymerase (PARP) inhibitor that blocks enzymes involved in repairing damaged DNA. It is intended for women with heavily pretreated ovarian cancer that is associated with defective BRCA genes.
    - The FDA approved Lynparza with a genetic test called BRACAnalysis CDx (Myriad Genetic Laboratories, Inc.), a companion diagnostic that will detect the presence of mutations in the BRCA genes in blood samples from patients with ovarian cancer.
- Approval of niraparib and rucaparib (Rubraca, Clovis Oncology Inc.), a poly ADP-ribose polymerase (PARP) inhibitor, for the maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.
    - Rubraca is indicated for the treatment of adult patients with deleterious BRCA mutation (germline and/or somatic)- associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies.

Prostate Cancer

NCCN guidelines for prostate cancer state germline testing should be considered in appropriate individuals where it is likely to impact the prostate cancer treatment and clinical trial options, management of risk of other cancers, and/or potential risk of cancer in family members. If criteria are met, germline multigene testing that includes at least BRCA1, BRCA2, ATM, PALB2, CHEK2, HOXB13, MLH1, MSH2, MSH6, and PMS2 is recommended.

Pancreatic Cancer

NCCN guidelines for pancreatic adenocarcinoma state pancreatic cancer is thought to have a familial component in approximately 10% of cases, and familial excess of pancreatic cancer is associated with high risk. The genetic basis of this inherited predisposition is not known in most cases, and as many as 80% of patients with a family history of pancreatic cancer have no known genetic cause. The genes most commonly associated with pathogenic germline alterations (PGAs) are BRCA1, BRCA2, ATM, PALB2, MLH1, MSH2, MSH6, PMS2, CDKN2A, and TP53. Germline mutations in the STK11 gene result in Peutz-Jeghers syndrome, in which individuals have gastrointestinal (GI) polyps and an increased risk for colorectal cancer. These individuals also have a highly elevated risk for developing pancreatic cancer, reported to be increased by as much as 132-fold. Furthermore, STK11 undergoes somatic mutation in approximately 5% of pancreatic cancers. Patients with Lynch syndrome also have an estimated 9- to 11-fold elevated risk for pancreatic cancer.

U.S. Food and Drug Administration (FDA) granted:

- Approval for Olaparib (LYNPARZA, AstraZeneca Pharmaceuticals LP) for the maintenance treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) metastatic pancreatic adenocarcinoma, as detected by an FDA-approved test, whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen.

Colorectal Cancer/ Polyposis Syndromes

Evidence from peer-reviewed literature and consensus from specialty organizations such as the American Gastroenterological Association and the National Cancer Institute indicate that genetic testing for LS pathogenic variants in affected patients is appropriate for individuals who meet either the Amsterdam II Criteria or Revised Bethesda Guidelines. Genetic testing of unaffected individuals is generally considered appropriate in those patients when they have a first- or second-degree relative with a known LS pathogenic variant. There is good evidence indicating that testing in these individuals may improve health outcomes. Clinical benefits include identifying patients who will require increased surveillance, determining best surveillance methods, and suggesting prophylactic, surgical options.

The American College of Gastroenterology recommends that all newly diagnosed colorectal cancers (CRCs) should be evaluated for mismatch repair deficiency. Analysis may be conducted by IHC testing for the MLH1, MSH2, MSH6, and PMS2 proteins and/or by MSI testing. Tumors that demonstrate loss of MLH1 should undergo BRAF testing or analysis for *MLH1* promoter hypermethylation. Individuals who have a personal history of a tumor showing evidence of mismatch repair deficiency (and no demonstrated BRAF pathogenic variant or hypermethylation of MLH1, a known family pathogenic variant associated with LS, or a risk of 5% or greater chance of LS based on risk prediction models should undergo genetic evaluation for LS.

The U.S. Multi-Society Task Force on Colorectal Cancer developed guidelines to assist health care providers with the appropriate provision of genetic testing and management of patients at risk for and affected with LS. Testing for MMR deficiency of newly diagnosed CRC should be performed. This can be done for all CRCs, for CRC diagnosed at age 70 years or younger, and for individuals older than age 70 years who have a family history of concern vis-a-vis LS. IHC analysis may be utilized to test for the MLH1, MSH2, MSH6, and PMS2 proteins, or testing for MSI may be performed. Tumors that demonstrate loss of MLH1 should undergo BRAF testing or analysis of MLH1-promoter hypermethylation.

The ASCO Clinical Practice Guideline endorsement of the European Society for Medical Oncology Clinical Practice Guideline addressing the familial risk of colorectal cancer recommends tumor testing for DNA mismatch repair (MMR) deficiency with IHC for MMR proteins and/or assessing MSI in all CRC patients. As an alternate strategy, tumor testing should be carried out in individuals with CRC who are under age 70 years, or individuals who are older than 70 years and who fulfill any of the revised Bethesda Guidelines. If loss of MLH1 or PMS2 protein expression is observed in the tumor, analysis of BRAF V600E pathogenic variant or analysis of methylation of the MLH1-promoter should be carried out first, to rule out a sporadic case. If the tumor is MMR-deficient and neither somatic BRAF pathogenic variant nor MLH1 promoter methylation is detected, testing for germline pathogenic variant is indicated. If loss of any of the other proteins (MSH2, MSH6, or PMS2) is observed, germline genetic testing should be carried out for the genes corresponding to the absent proteins (e.g., MSH2, MSH6, EPCAM, PMS2, or MLH1). Full germline genetic testing for LS should include DNA sequencing and large rearrangement analysis.

The U.S. Multi-Society Task Force on Colorectal Cancer 2022 guidelines for gastrointestinal hamartomatous polyposis syndromes recommends genetic screening when any of the following are present: two or more lifetime hamartomatous polyps, a family history of hamartomatous polyps, or a cancer associated with a hamartomatous polyposis syndrome in first or second-degree relatives. If genetic testing is indicated, a multigene panel test should be performed.

The NCCN Clinical Practice Guidelines for Genetic/Familial High-Risk Assessment: Colorectal recommend that MSI testing be performed on all patients with colorectal cancers and endometrial cancers, regardless of age or family history, to identify individuals at risk for LS. The NCCN guidelines go on to state that the cost-effectiveness of this approach has been confirmed for colorectal cancer and that the approach has been endorsed by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP), the Centers for Disease Control and Prevention (CDC), the U.S. Multi-Society Task Force on Colorectal Cancer, and the European Society for Medical Oncology (ESMO). NCCN also recommends tumor screening for MMR deficiency for sebaceous neoplasms, small bowel, ovarian, gastric, pancreatic, biliary tract, brain, bladder, urothelial, and adrenocortical cancers diagnosed at any age. If a tumor is found to be MSI-high the patient should be referred for germline MMR testing.

Cowden Syndrome

Pilarski et al. (2011) conducted a systematic review related to the clinical features reported in individuals with a PTEN mutation and proposed revised diagnostic criteria. The authors concluded that there was insufficient evidence to support

inclusion of benign breast disease, uterine fibroids, or genitourinary malformations as diagnostic criteria. There was sufficient evidence to include autism spectrum disorders, colon cancer, esophageal glycogenic acanthosis, penile macules, renal cell carcinoma, testicular lipomatosis and vascular anomalies, and these clinical features are included in Cowden syndrome testing's minor criteria under NCCN guidelines.

The International Cowden Consortium criteria for Cowden syndrome have been updated several times since 1996 and are the basis for the NCCN 2022 criteria for PTEN mutation testing. The criteria have been divided into three categories depending on diagnostic features, major features, and minor features associated with Cowden's syndrome. In addition, a first-degree relative of an affected individual with one or more major, or two or more minor criteria, along with a relative diagnosed with Cowden syndrome or Bannayan-Riley-Ruvalcaba syndrome (who has not been tested) would also meet the threshold for PTEN testing.

Li-Fraumeni Syndrome

The NCCN guidelines for genetic/familial high-risk assessment of breast and ovarian cancers utilize both the classic Li Fraumeni clinical criteria and the Chompret criteria when recommending genetic testing for a mutation in the TP53 gene. The NCCN panel also included lung bronchoalveolar cancer and leukemia, as one of the core tumor types. Testing individuals with choroid plexus carcinoma, diagnosed at any age, has been recommended regardless of family history based upon high incidence of TP53 mutations found in patients with this rare form of brain tumor. Women with early-onset breast cancer (diagnosed by or before age 31 years) with or without core history of tumor types, are another group for whom TP53 mutation testing may be considered. A member of a family with a known TP53 mutation is considered to be at sufficient risk to warrant gene mutation testing, even in the absence of any other risk factors.

Hereditary Diffuse Gastric Cancer

The NCCN Gastric Cancer Guidelines recommend genetic testing for a mutation in the CDH1 gene for HDGC. The recommended criteria include personal/family history of gastric cancer, lobular breast cancer, Māori ethnicity, and personal or family history of a cleft lip/palate. The International Gastric Cancer Linkage Consortium (IGCLC) published a set of clinical criteria for genetic testing starting in 1999 with multiple updates, the most recent being 2020. The 2020 criteria, published by Blair et al., expanded selection criteria mainly through changes to age restrictions and inclusion of Māori ethnicity, personal or family history of a cleft lip/palate, and Gastric in situ signet ring cells and/or pagetoid spread of signet ring cells under 50 years old. Approximately 13% of New Zealand Māori with advanced DGC have pathogenic germline CDH1 variants and it is now recommended that all Māori with confirmed DGC have CDH1 genetic testing completed. Cleft lip/palate has been described in some HDGC families and is also included in CDH1 genetic testing guidelines. Prophylactic total gastrectomy remains the recommended option for gastric cancer risk management in pathogenic CDH1 variant carriers. Women with CDH1 mutations are at an increased risk for lobular breast cancer and NCCN recommends screening with breast MRI starting at age 30 years, and a discussion of the option of risk-reducing mastectomy.

Familial Medullary Thyroid Carcinoma (FMTC/MTC)

Genetic testing for mutations in the RET gene is considered part of standard management of first-degree relatives of affected individuals. Persons who are mutation-positive may undergo thyroidectomy as a preventive measure, followed by biochemical screening for the other endocrine tumors. Genetic testing of unaffected relatives is most useful when a germline mutation has been identified in the affected family member.

NCCN guidelines for Thyroid Carcinoma state germline testing for RET proto-oncogene mutations with genetic counseling by a physician or genetic counselor is recommended for all patients with newly diagnosed MTC or clinically suspected sporadic MTC. If a germline RET mutation is found, then mutation testing should also be done for family members. There is sufficient evidence to conclude that genetic tests for germline point mutations in the RET gene can identify individuals with an inherited susceptibility for medullary thyroid cancer earlier and long before clinical symptoms or signs are noted. Test results affect patient management by prompting thyroidectomy or continued biochemical monitoring in affected patients, and by prompting discontinuation of monitoring in patients who test negative.

Multigene Panel Testing

The NCCN guidelines on Genetic/Familial High-Risk Assessment: Breast and Ovarian, Gastric Cancer include genetic testing panels using next generation sequencing for hereditary breast, ovarian and other cancers. The guidelines state that these panels are intended for individuals who have tested negative for high penetrance genes (BRCA1 and BRCA2), as well as for those whose family history is suggestive of more than one syndrome. Limitations of these panels include unknown percentage of variants of unknown significance, uncertainty of the level of risk associated with most of these genes, and lack of clear guidelines on risk management of carriers of some of these mutations as well as the moderate-penetrant genes. NCCN recommends that these multigene hereditary cancer panels should only be ordered in consultation with a cancer genetics professional.

NCCN guidelines for genetic/familial high-risk assessment for breast, ovarian, pancreatic and colorectal cancers state the introduction of multigene testing for hereditary forms of cancer has rapidly altered the clinical approach to testing affected, at-risk patients and their families. When more than one gene can explain an inherited cancer syndrome, multigene testing is more efficient than single-gene testing, or sequential single syndrome testing. There is also a role for multigene testing in individuals who have tested negative (indeterminate) for a single syndrome, but personal or family history remains strongly suggestive of an inherited susceptibility. Chance of identifying pathogenic variants in multiple actionable genes that could impact screening and management for the individual and family members that may be missed using cancer syndrome-specific panels. Chances of finding a VUS or pathogenic variant with uncertain clinical management increase as the number of genes included in the multigene panel increase. Multigene testing can include "intermediate" penetrant (moderate risk) genes. For many of these genes, there are limited data on the degree of cancer risk and there are no clear guidelines on risk management for carriers of pathogenic variants. Not all genes included on available multigene tests are necessarily clinically actionable. It is for these and other reasons that multigene testing is ideally offered in the context of professional genetic expertise for pre- and post-test counseling. Individuals with the recommended expertise include certified genetic counselors, as well as clinicians who have had extensive training and/or experience in identification and management of hereditary syndromes. Multi-gene testing is not recommended when there is an individual from a family with a known pathogenic/ likely pathogenic variant and there is no other reason for multi-gene testing.

The introduction of multi-gene testing for hereditary forms of cancer has rapidly altered the clinical approach to testing at-risk patients and their families. Multi-gene testing simultaneously analyzes a set of genes that are associated with a specific family cancer phenotype or multiple phenotypes. Multi-gene testing may include syndrome-specific tests (i.e., panels that test for only one syndrome like Lynch syndrome, adenomatous polyposis), cancer-specific tests (i.e., panels that test for more than one gene associated with a specific type of cancer like CRC), and comprehensive cancer panels (i.e., panels that test for more than one gene associated with multiple cancers or cancer syndromes). Multi-gene testing with panels that include genes associated with LS, as well as other highly penetrant genes associated with CRC, may be cost-effective, and this approach may detect pathogenic variants not found in single-gene testing. Multi-gene testing may also be considered for those who tested negative (indeterminate) for one particular syndrome, but whose personal and family history is strongly suggestive of an inherited susceptibility. Germline multi-gene panel testing should include at minimum the following CRC risk-associated genes: APC, MUTYH, MLH1, MSH2, MSH6, PMS2, EPCAM, BMPR1A, SMAD4, PTEN, STK11, and TP53. When more than one gene can explain an inherited cancer syndrome, multigene testing is more efficient than single-gene testing, or sequential single syndrome testing.

According to NCCN Multi-gene testing is not recommended when: 1) there is an individual from a family with a known P/LP variant and there is no other reason for multigene testing; and 2) the patient's family history is strongly suggestive of a known hereditary syndrome. In these scenarios, syndrome-specific panels may be considered. For patients whose personal history is not suspicious for a polyposis syndrome and who were diagnosed with CRC ≥50 years with no known MMR deficiency in the tumor, multigene testing may be considered (category 2B). Otherwise, tumor and family history-based criteria for evaluation of Lynch syndrome is recommended for these patients.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*

- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*
- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).*

CPT Codes

Code	Description
81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (i.e., detection of large gene rearrangements)
81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
81165	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81166	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
81167	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
81201	APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
81202	APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
81203	APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants
81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)
81212	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
81215	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
81216	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81217	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
81288	MLH1 (mutl homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis

Code	Description
81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81293	MLH1 (mutl homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81294	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81295	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81296	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81297	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81298	MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81299	MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81300	MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81301	Microsatellite instability analysis (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (e.g., BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
81307	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; full gene sequence
81308	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; known familial variant
81317	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81318	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81319	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81321	PTEN (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
81322	PTEN (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant
81323	PTEN (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant

Code	Description
81351	TP53 (Tumor Protein 53) (e.g., Li-Fraumeni syndrome) gene analysis; full gene sequence
81352	TP53 (Tumor Protein 53) (e.g., Li-Fraumeni syndrome) gene analysis; targeted sequence analysis (e.g., 4 oncology)
81353	TP53 (Tumor Protein 53) (e.g., Li-Fraumeni syndrome) gene analysis; known familial variant
81401	Molecular Pathology Procedure Level 2
81404	Molecular Pathology Procedure Level 5
81405	Molecular Pathology Procedure Level 6
81406	Molecular Pathology Procedure Level 7
81407	Molecular Pathology Procedure Level 8
81408	Molecular Pathology Procedure Level 9
81432	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53
81433	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer) duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11
81435	Hereditary colon cancer disorders (e.g., 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 (e.g., 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
81479	Unlisted molecular pathology procedure
0101U	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated (15 genes [sequencing and deletion/duplication], EPCAM and GREM1 [deletion/duplication only]) (e.g., ColoNext, Ambry Genetics)
0102U	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated (17 genes [sequencing and deletion/duplication]) (e.g., BreastNext, Ambry Genetics)

Code	Description
0103U	Hereditary ovarian cancer (e.g., hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated (24 genes [sequencing and deletion/duplication], EPCAM [deletion/duplication only]) (e.g., OvaNext, Ambry Genetics)
0129U	Hereditary breast cancer–related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53) (BRCAPlus by Ambry Genetics)
0130U	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), targeted mRNA sequence analysis panel (APC, CDH1, CHEK2, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, and TP53) (List separately in addition to code for primary procedure) (Use 0130U in conjunction with 81435, 0101U) (+RNAinsight™ for ColoNext® by Ambry Genetics)
0131U	Hereditary breast cancer–related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (13 genes) (List separately in addition to code for primary procedure) (Use 0131U in conjunction with 81162, 81432, 0102U) (+RNAinsight™ for BreastNext® by Ambry Genetics
0132U	Hereditary ovarian cancer–related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (17 genes) (List separately in addition to code for primary procedure)(Use 0132U in conjunction with 81162, 81432, 0103U) (+RNAinsight™ for OvaNext® by Ambry Genetics)
0133U	Hereditary prostate cancer–related disorders, targeted mRNA sequence analysis panel (11 genes) (List separately in addition to code for primary procedure) (Use 0133U in conjunction with 81162) (*RNAinsight™ for ProstateNext, Ambry Genetics)
0134U	Hereditary pan cancer (e.g., hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (18 genes) (List separately in addition to code for primary procedure) (Use 0134U in conjunction with 81162, 81432, 81435) (+RNAinsight™ for CancerNext®, Ambry Genetics)
0135U	Hereditary gynecological cancer (e.g., hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (12 genes) (List separately in addition to code for primary procedure) (Use 0135U in conjunction with 81162) (+RNAinsight™ for GYNPlus®, Ambry Genetics)
0136U	ATM (ataxia telangiectasia mutated) (e.g., ataxia telangiectasia) mRNA sequence analysis (List separately in addition to code for primary procedure) (Use 0136U in conjunction with 81408) (+RNAinsight™ for ATM, Ambry Genetics)
0137U	PALB2 (partner and localizer of BRCA2) (e.g., breast and pancreatic cancer) mRNA sequence analysis (List separately in addition to code for primary procedure) (Use 0137U in conjunction with 81406) (RNAinsight™ for PALB2, Ambry Genetics)

Code	Description
0138U	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) mRNA sequence analysis (List separately in addition to code for primary procedure) (Use 0138U in conjunction with 81162 (RNAinsight™ for BRCA1/2, Ambry Genetics
0157U	APC (APC regulator of WNT signaling pathway) (e.g., familial adenomatosis polyposis [FAP]) mRNA sequence analysis (List separately in addition to code for primary procedure) (CustomNext + RNA: APC, Ambry Genetics)
0158U	MLH1 (mutL homolog 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure) (CustomNext + RNA: MLH1, Ambry Genetics)
0159U	MSH2 (mutS homolog 2) (e.g., hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure) (CustomNext + RNA: MSH2, Ambry Genetics)
0160U	MSH6 (mutS homolog 6) (e.g., hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure) (CustomNext + RNA: MSH6, Ambry Genetics)
0161U	PMS2 (PMS1 homolog 2, mismatch repair system component) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure) (CustomNext + RNA: PMS2, Ambry Genetics)
0162U	Hereditary colon cancer (Lynch syndrome), targeted mRNA sequence analysis panel (MLH1, MSH2, MSH6, PMS2) (List separately in addition to code for primary procedure) (CustomNext + RNA: Lynch (MLH1, MSH2, MSH6, PMS2), Ambry Genetics)
0235U	PTEN (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions (Genomic Unity® PTEN Analysis, Variantyx Inc)
0238U	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 (Genomic Unity Lynch Syndrome Analysis, Variantyx Inc)

HCPCS Codes

Code	Description
S3840	DNA analysis for germline mutations of the RET proto-oncogene for susceptibility to multiple endocrine neoplasia type 2

ICD10 Codes

Code	Description
C18.0-C18.9	Malignant neoplasm of colon (code range)

Code	Description
C19	Malignant neoplasm of rectosigmoid junction
C25.0-C25.9	Malignant neoplasm of pancreas (code range)
C50.011-C50.929	Malignant neoplasm of breast (code range)
C56.1-C56.9	Malignant neoplasm of ovary (code range)
C61	Malignant neoplasm of prostate
C73	Malignant neoplasm of thyroid gland
C79.60-C79.62	Secondary malignant neoplasm of ovary (code range)
C79.81	Secondary malignant neoplasm of breast
C79.82	Secondary malignant neoplasm of genital organs
C79.89-C79.9	Secondary malignant neoplasm of other specified and unspecified sites (code range)
D01.0-D01.3	Carcinoma in situ of other and unspecified digestive organs (code range)
D05.00-D05.02	Lobular carcinoma in situ of breast (code range)
D05.10-D05.12	Intraductal carcinoma in situ of breast (code range)
D05.80-D05.92	Carcinoma in situ of breast, specified, unspecified (code range)
D07.30-D07.39	Carcinoma in situ of other and unspecified female genital organs (code range)
D07.5	Carcinoma in situ of prostate
D09.3-D09.8	Carcinoma in situ of thyroid and other endocrine glands and other specified sites (code range)
D12.0-D12.9	Benign neoplasm of colon, rectum, anus, and anal canal (code range)
D37.2-D37.5	Neoplasm of uncertain behavior of digestive organs (code range)
D40.0	Neoplasm of uncertain behavior of prostate
D49.0	Neoplasm of unspecified behavior of digestive system
K63.5	Polyp of colon
Z15.01	Genetic susceptibility to malignant neoplasm of breast
Z15.02	Genetic susceptibility to malignant neoplasm of ovary
Z15.03	Genetic susceptibility to malignant neoplasm of prostate
Z31.5	Encounter for procreative genetic counseling
Z80.0	Family history of malignant neoplasm of digestive organs
Z80.3	Family history of malignant neoplasm of breast
Z80.41	Family history of malignant neoplasm of ovary
Z80.42	Family history of malignant neoplasm of prostate
Z80.8	Family history of malignant neoplasm of other organs or systems

Code	Description
Z85.07	Personal history of malignant neoplasm of pancreas
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
Z85.3	Personal history of malignant neoplasm of breast
Z85.43	Personal history of malignant neoplasm of ovary
Z85.46	Personal history of malignant neoplasm of prostate
Z85.850	Personal history of malignant neoplasm of thyroid

REFERENCES

Abu-Ghazaleh N, et al. Worldwide prevalence of Lynch syndrome in patients with colorectal cancer: Systematic review and meta-analysis. Genetics in Medicine 2022 Jan;24:971-985.

Adar T, et al. Universal screening of both endometrial and colon cancers increases the detection of Lynch syndrome. Cancer 2018 Aug;124(15):3145-3153.

Adib E, et al. CDH1 germline variants are enriched in patients with colorectal cancer, gastric cancer, and breast cancer. Br J Cancer 2022 Mar; 126(5): 797–803.

Alvarado M, et al. Prevalence of mutations in a diverse cohort of 3162 women tested via the same multigene cancer panel in a managed care health plan. J Community Genet 2020 Jul; 11(3): 359–366.

*American College of Medical Genetics/American Society of Human Genetics. Genetic testing for colon cancer: joint statement of the American College of Medical Genetics and American Society of Human Genetics. Genet Med 2000 Nov/Dec;2(6):1-5.

American College of Medical Genetics and Genomics. ACMG technical standards for clinical genetics laboratories. 2021 [https://www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/Genetics_Lab_Standards/ACMG/Medical-Genetics-Practice-Resources/Genetics_Lab_Standards.aspx?hkey=0e473683-3910-420c-9efb-958707c59589] accessed 11/27/23.

American College of Obstetricians and Gynecologists, Practice Bulletin #103: Hereditary breast and ovarian cancer syndrome. Obstet Gynecol 2009;113(4):957-66.

*American Society of Breast Surgeons. Official Statement: Consensus guideline on genetic testing for hereditary breast cancer. 2019. [https://www.breastsurgeons.org/resources/statements] accessed 11/27/23.

*American Society of Clinical Oncology. American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility (adopted on March 1, 2003 by the American Society of Clinical Oncology). J Clin Oncol 2003 Jun;21(12):2397-414.

An JY, et al. A multi-cohort study of the prognostic significance of microsatellite instability or mismatch repair status after recurrence of resectable gastric cancer. Cancer Res Treat 2020;52(4):1153-1161.

*Antoniou A, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 2003 May;72(5):1117-30.

Bai H, et al. Evaluation of concordance between deficient mismatch repair and microsatellite instability testing and their association with clinicopathological features in colorectal cancer. Cancer Manag Res 2020;12:2863–2873.

*Blair V, et al. Hereditary diffuse gastric cancer: updated clinical practice guidelines. Lancet Oncol 2020 Aug; 21(8): e386–e397.

*Boland CR, et al. Diagnosis and management of cancer risk in the gastrointestinal hamartomatous polyposis syndromes: recommendations for the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2022 Jun;162(7):2063-2085.

*Bolton KL, et al. Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. JAMA 2012 Jan 25;307:382-90.

*Brauckhoff M, et al. Multiple endocrine neoplasia 2B syndrome due to codon 918 mutation: clinical manifestation and course in early and late onset disease. World J Surg 2004 Dec;28(12):1305-11.

Breast Cancer Association Consortium. Breast cancer risk genes- association analysis in more than 113,000 women, N Engl J Med 2021 Feb 4;384(5):428-439.

Cioffi A, et al. Prevalence of Germline BRCA1/2 Variants in Ashkenazi and Non-Ashkenazi Prostate Cancer Populations: A Systematic Review and Meta-Analysis. Cancers (Basel) 2023 Jan 2;15(1):306.

Cummings S, et al. Cancer risk associated With PTEN pathogenic variants identified using multigene hereditary cancer panel testing. JCO Precis Oncol 2023 Jan;7:e2200415.

*Daly PA, et al. Predictive testing for BRCA1 and 2 mutations: a male contribution. Ann Oncol 2003 Apr;14(4):549-53.

Deshpande M, et al. Gynecological cancers caused by deficient mismatch repair and microsatellite instability. Cancers (Basel) 2020 Nov;12(11):3319.

Duraturo F, et al. Genetics, diagnosis, and treatment of Lynch syndrome: old lessons and current challenges (review). Oncol Lett 2019 Mar;17(3):3048-3054.

*Eng C. PTEN Hamartoma Tumor Syndrome (PHTS). Gene Reviews. Initial Posting 2001 Nov 29; Last update: February 11, 2021. Funded by the NIH. [http://www.ncbi.nlm.nih.gov/books/NBK1488/] accessed 11/27/23.

*Eng C. Will the real Cowden syndrome please stand up: revised diagnostic criteria. J Med Genet 2000;37(11):828-30.

Evrard C, et al. Microsatellite instability: diagnosis, heterogeneity, discordance, and clinical impact in colorectal cancer. Cancers (Basel) 2019 Oct;11(10):1567.

*Frank-Raue K, et al. Long-term outcome in 46 gene carriers of hereditary medullary thyroid carcinoma after prophylactic thyroidectomy: impact of individual RET genotype. Eur J Endocrinol 2006 Aug;155(2):229-36.

*Giardiello FM, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-Society Task Force on Colorectal Cancer. Dis Colon Rectum 2014 Aug;57(8):1025-48.

Haidle JL, Howe JR. Juvenile polyposis syndrome. Funded by NIH. Developed by the University of Washington, Seattle. Updated Feb 3, 2022 [http://www.ncbi.nlm.nih.gov/books/NBK1469/] accessed 11/27/23.

Hampel H, et al. Assessment of tumor sequencing as a replacement for Lynch syndrome screening and current molecular tests for patients with colorectal cancer. JAMA Oncol 2018 Jun 1;4(6):806-813.

Hu C, et al. A population-based study of genes previously implicated in breast cancer. N Engl J Med 2021 Feb 4;384(5):440-451.

Jasperson KW, et al. APC-associated polyposis conditions. Funded by NIH. Developed by the University of Washington, Seattle. Updated May 12, 2022 [http://www.ncbi.nlm.nih.gov/books/NBK1345/] accessed 11/27/23.

Jiang W, et al. Universal screening for Lynch syndrome in a large consecutive cohort of Chinese colorectal cancer patients: high prevalence and unique molecular features. Int J Cancer 2019 May;144(9):2161-2168.

Jiang W, et al. Universal germline testing among patients with colorectal cancer: clinical actionability and optimised panel. J Med Genet 2022 Apr;59(4):370-376.

Jorge S, et al. Simultaneous germline, and somatic sequencing in ovarian carcinoma: mutation rate and impact on clinical decision -making. Gyn Oncol 2020 Mar;156(3):517-522.

*Judkins T, et al. Clinical significance of large rearrangements in BRCA1 and BRCA2. Cancer 2012;118:5210-6.

Kahn RM, et al. Universal endometrial cancer tumor typing: how much has immunohistochemistry, microsatellite instability, and MLH1 methylation improved the diagnosis of lynch syndrome across the population? Cancer 2019 Sep;125(18):3172-3183.

Katz SJ, et al Association of attending surgeon with variation in the receipt of genetic testing after diagnosis of breast cancer. JAMA Surg 2018 Oct 1;153(10):909-916.

Kohlmann W, et al. Hereditary nonpolyposis colon cancer. Funded by the NIH. Developed at the University of Washington, Seattle. Updated Feb 4, 2021 [http://www.ncbi.nlm.nih.gov/books/NBK1211/] accessed 11/27/23.

*Kouvaraki MA, et al. RET proto-oncogene: a review and update of genotype-phenotype correlations in hereditary medullary thyroid cancer and associated endocrine tumors. Thyroid 2005 Jun;15(6):531-44.

Kurian AW, et al. Association of germline genetic testing results with locoregional and systemic therapy in patients with breast cancer. JAMA Oncol 2020;6(4):e196400.

*Kurian AW, et al. Breast cancer risk for noncarriers of family specific BRCA1 and BRCA2 mutations: findings from the breast cancer family registry. J Clin Oncol 2011 Dec 1;29(34):4505-9.

LaDuca H, et al. A clinical guide to hereditary cancer panel testing: evaluation of gene-specific cancer associations and sensitivity of genetic testing criteria in a cohort of 165,000 high-risk patients. Genet Med 2020;22(2):407-415.

*Leenen CH, et al. Cost-effectiveness of routine screening for Lynch syndrome in colorectal cancer patient sup to 70 years of age. Genet Med 2016 Oct;18(10):966-73.

*Leenen CH, et al. Prospective evaluation of molecular screening for Lynch syndrome in patients with endometrial cancer < 70 years. Gynecol Oncol 2012;125(2):414-20.

Lerner BA, et al. Simplified and more sensitive criteria for identifying individuals with pathogenic CDH1 variants. J Med Genet 2022 Jan; 0: 1–5.

Lindner AK, et al. Lynch syndrome: its impact on urothelial carcinoma Int J Mol Sci 2021 Jan;22(2):531.

Lu K, et al. Genetic variation and the role of multigene panel testing for hereditary breast cancer: a single-institution experience. Cureus 2021 Apr 22;13(4):e14637.

Manchanda R, et al. Cost-effectiveness of population based BRCA testing with varying Ashkenazi Jewish ancestry. Am J Obstet Gynecol 2017 Nov;217(5):578.e1-578.e12.

Mao R, et al. Genetic testing for inherited colorectal cancer and polyposis, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genetics in Medicine 2021 Jun; 23:1807–1817.

McGarrity TJ, et al. Peutz-Jeghers Syndrome. Funded by NIH. Developed by the University of Washington, Seattle. Updated Sep 2, 2021 [http://www.ncbi.nlm.nih.gov/books/NBK1266/] accessed 11/27/23.

*Meijers-Heijboer H, et al. Use of genetic testing and prophylactic mastectomy and oophorectomy in women with breast or ovarian cancer from families with a BRCA1 or BRCA2 mutation. J Clin Oncol 2003 May;21(9):1675-81.

*Mitra AV, et al. Targeted prostate cancer screening in men with mutations in BRCA1 and BRCA2 detects aggressive prostate cancer: Preliminary analysis of the results of the IMPACT study. BJU Int 2011;107:28-39.

Mitric C, et al. Mismatch-repair deficiency, microsatellite instability, and lynch syndrome in ovarian cancer: A systematic review and meta-analysis. Gynecol Oncol 2023 Mar;170:133-142.

*Moo-Young TA, et al. Sporadic and familial medullary thyroid carcinoma: state of the art. Surg Clin N Am 2009 Oct;89(5):1193-204.

*Moore SE, et al. Familial medullary carcinoma prevention, risk evaluation, and RET in children of families with MEN2. J Pediatr Surg 2007 Feb;42(2):326-32.

*Moslim Ma, et al. Early genetic counseling and detection of CDH1 mutation in asymptomatic carriers improves survival in hereditary diffuse gastric cancer. Surgery 2018 Oct;164(4):754-759.

Narayan P, et al. Partner and localizer of BRCA2 (PALB2) pathogenic variants and ovarian cancer: A systematic review and meta-analysis. Gynecol Oncol 2023 Aug 29;177:72-85.

National Cancer Institute (NCI). US National Institute of Health (NIH). Genetics of breast and ovarian cancer (PDQ®). Last modified: 08 July 2021 [http://www.cancer.gov/cancertopics/pdq/genetics/breast-and-ovarian/HealthProfessional] accessed 11/27/23.

*National Center for Health Professional Education in Genetics. Core Competencies in Genetics for Health Professionals. 2007 Sep; 3rd ed.

*National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Breast Cancer. V.4.2023 March 23, 2023 [https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf] accessed 11/27/23.

*National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Gastric Cancer. V.2.2023 August 29, 2023 [https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf] accessed 11/27/23.

*National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. V.2.2024.September 27, 2023 [https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf] accessed 11/27/23.

*National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Genetic/Familial High-Risk Assessment: Colorectal. V.2.2023. October 30, 2023 [https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf] accessed 11/27/23.

*National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer. V.2.2023 June 2, 2023 [https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf] accessed 11/27/23.

*National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Pancreatic Adenocarcinoma. V.2.2023 June 19, 2023 [https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf] accessed 11/27/23.

*National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Prostate Cancer. V.4.2023 September 7, 2023 [https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf] accessed 11/27/23.

*National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Thyroid Carcinoma. V.4.2023 August 16, 2023 [https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf] accessed 11/27/23.

National Office of Public Health Genomics, Centers for Disease Control and Prevention. Fact sheet on genetic testing for breast and ovarian cancer susceptibility. Last updated: 06/20/2023. [https://www.cdc.gov/genomics/disease/breast_ovarian_cancer/] accessed 11/27/23.

National Office of Public Health Genomics, Centers for Disease Control and Prevention. Genetic counseling and evaluation for BRCA 1/2. Last updated 06/20/23. [https://www.cdc.gov/genomics/disease/breast_ovarian_cancer/counseling.htm] accessed 11/27/23.

Oh M, et al. The association of BRCA1 and BRCA2 mutations with prostate cancer risk, frequency, and mortality: a meta-analysis. Prostate 2019 Jun;79(8):880-895.

Ohmoto A, et al. Genomic features, and clinical management of patients with hereditary pancreatic cancer syndromes and familial pancreatic cancer. Int J Mol Sci 2019 Jan;20(3):piiE561.

*Petrucelli N, et al. BRCA1 and BRCA2 Hereditary Breast and Ovarian Cancer. Gene Reviews Initial Posting 1998 Sep 04; Last update: September 21, 2023. Funded by the NIH.[http://www.ncbi.nlm.nih.gov/books/NBK1247/] accessed 11/27/23.

*Pilarski R, et al. Predicting PTEN mutations: an evaluation of Cowden syndrome and Bannayan-Rile-Ruvalcaba syndrome clinical features. J Med Genet 2011;48(8):505-512.Rath MG, et al. Prevalence of TP53 germline mutations in HER2+ breast cancer patients. Breast Cancer Res Treat 2013;139(1):193-8.

Pilarski R. The role of BRCA testing in hereditary pancreatic and prostate cancer families. Am Soc Clin Oncol Educ Book 2019 Jan;39:79-86.

*Poumpouridou N, et al. Hereditary breast cancer: beyond BRCA genetic analysis; PALB2 emerges. Clin Chem Lab Med 2011 Dec;50(3):423.

Puerto M, et al. Updates on therapy for medullary thyroid cancer in 2021. Annales d'Endocrinologie 2022;83:114-118.

*Quayle FJ, et al. Medullary thyroid carcinoma: including MEN 2A and MEN 2B syndromes. J Surg Oncol 2005 Mar 1;89(3):122-9.

Roberts ME, et al. Comparison of CDH1 penetrance estimates in clinical ascertained families vs families ascertained for multiple gastric cancers. JAMA Oncol 2019;5(9):1325-1331.

Robson ME, et al. American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility. J Clin Oncol 2015 Nov 1;33(31):3660-3667.

Rosen MN, et al. BRCA mutated pancreatic cancer: a change is coming. World J Gastroenterol 2021 May;27(17):1943-1958.

Salyer C, et al. Clinical characteristics, and outcomes in elderly women with BRCA1 and BRCA2 mutations. Gynecol Oncol 2019 Aug;154(2):374-378.

Samadder NJ, et al. Comparison of universal genetic testing vs guidelines-directed targeted testing for patients with hereditary cancer syndrome. JAMA Oncol 2021 Feb;7(2):230-237.

*Schneider K, et al. Li-Fraumeni Syndrome. Gene Reviews. Initial Posting 1999 Jan 19; Last update: November 21, 2019. Funded by the NIH. [http://www.ncbi.nlm.nih.gov/books/NBK1311/] accessed 11/27/23.

Shin HC, et al. Detection of germline mutations in breast cancer patients with clinical features of hereditary cancer syndrome using a multi-gene panel test. Cancer Res Treat 2020 Jul; 52(3): 697–713.

Sinicrope FA. Lynch syndrome-associated colorectal cancer. N Engl J Med 2018;379(8):764-773.

Slavin TP, et al. Genetics of gastric cancer: what do we know about the genetic risks? Transl Gastroenterol Hepatol 2019 Jul 29;4:55.

Suerink M, et al. Prevalence of mismatch repair deficiency and Lynch syndrome in a cohort of unselected small bowel adenocarcinomas. J Clin Pathol 2021 Nov;74(11):724-729.

*Stadler ZK, et al. Prevalence of BRCA1 and BRCA2 mutations in Ashkenazi Jewish families with breast and pancreatic cancer. Cancer 2012 Jan 15;118(2):494-9.

*Stoffel EM, et al. Hereditary colorectal cancer syndromes: American Society of Clinical Oncology Clinical Practice guideline endorsement of the familial risk – colorectal cancer: European Society for Medical Oncology clinical practice guidelines. J Clin Oncol 2015 Jan;33(2):209-17.

*Syngal S, et al. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol 2015 Feb;110(2):223-62.

U.S. Preventive Services Task Force. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women: U.S. Preventive Services Task Force Final Recommendation Statement. 2019 Aug 20. [https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/brca-related-cancer-risk-assessment-genetic-counseling-and-genetic-testing] accessed 11/27/23.

Witjes VM, et al. Probability of detecting germline BRCA1/2 pathogenic variants in histological subtypes of ovarian carcinoma. A meta-analysis. Gynecol Oncol 2022 Jan;164(1):221-230

Yadav S, et al. Evaluation of germline genetic testing criteria in a hospital-based series of women with breast cancer. J Clin Oncol 2020 May 1;38(13):1409-1418.

Yadav S, et al. Germline pathogenic variants in cancer predisposition genes among women with invasive lobular carcinoma of the breast. Jour of Clin Onc 2021 Dec; 30(35): 3918-3926.

Yadav S, et al. Racial and ethnic differences in multigene hereditary cancer panel test results for women with breast cancer. J Natl Cancer Inst 2020 Nov 4 [Epub ahead of print].

Yang S, et al. Underdiagnosis of hereditary breast and ovarian cancer in Medicare patients: genetic testing criteria miss the mark. Ann Sug Oncol 2018;25(10):2925-2931.

Young EL, et al. Pancreatic cancer as a sentinel for hereditary cancer predisposition. BMC Cancer 2018;18:697.

*Key Article

KEY WORDS

Hereditary breast and ovarian cancer syndrome (HBOC), Cowden syndrome, li Fraumeni syndrome, hereditary diffuse gastric cancer, lynch syndrome, adenomatous polyposis syndromes, familial adenomatous polyposis (FAP), attenuated familial adenomatous polyposis (AFAP), MUTYH-associated polyposis (MAP)), and hamartomatous polyposis syndromes, peutz-jeghers syndrome (PJS), and juvenile polyposis syndrome (JPS), familial thyroid cancer, Medullary thyroid cancer, RET proto-oncogene, Thyroid cancer, CancerNext, MyRisk Hereditary Cancer.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a Local Coverage Determination (LCD) for Molecular Pathology Procedures (L35000). Please refer to the following LCD website for Medicare Members:

https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=35000&ver=138&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=Active&bc=AAgAAAQAgAAA&= accessed 11/27/23.

There is currently a Local Coverage Article (LCA) for Billing and Coding: Molecular Pathology Procedures (A56199). Please refer to the following LCA website for Medicare Members:

https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=56199&ver=95&LCDId=35000&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=Active&bc=AAgAAAQAgAAA&= accessed 11/27/23.