MEDICAL POLICY

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Medical Policy Title	**Germline Genetic Testing for Hereditary Cancers**
Policy Number	**2.02.60**
Current Effective Date	**April 16, 2026**
Next Review Date	**April 2027**

Our medical policies are guides to evaluate technologies or services for medical necessity. Criteria are established through the assessment of evidence based, peer-reviewed scientific literature, and national professional guidelines. Federal and state law(s), regulatory mandates and the member's subscriber contract language are considered first in the determination of a covered service. (Link to Product Disclaimer)

This policy does not address preimplantation genetic testing.

POLICY STATEMENT(S)

I. 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 individuals (an individual who does not have cancer) should be considered when meeting specific syndrome criteria below. (See Policy Guideline VI)

F. Individuals with limited family history (e.g., fewer than two (2) 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 meets criteria for specific genetic testing for susceptibility **ANY** of the following:

1. Breast cancer, refer to Policy Statement VI.A;
2. Ovarian cancer, refer to Policy Statement VI.B;
3. Pancreatic cancer, refer to Policy Statement VI.C;
4. Prostate cancer, refer to Policy Statement VI.D;

5. Colorectal cancer syndromes, refer to Policy Statement VI.E;
6. Cowden syndrome, refer to Policy Statement VI.F;
7. Li Fraumeni Syndrome, refer to Policy Statement VI.G;
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. Multigene panel testing (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. 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).

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. 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. Testing for a variant of unknown significance discovered in a family member, is considered **investigational**.

VI. 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;

b. Diagnosed at **any age** with **ONE** of the following:

i. To aid in systemic treatment decisions using PARP inhibitors for metastatic breast cancer;

ii. To aid in adjuvant treatment decisions with Olaparib for high-risk, HER2-negative breast cancer;

iii. Triple negative breast cancer (ER-/PR-/HER2-);

iv. Multiple primary breast cancers (synchronous or metachronous);

v. Lobular breast cancer with personal or family history of diffuse gastric cancer (see Policy Statement II.H);

vi. Male breast cancer;

vii. Ashkenazi Jewish ancestry;

viii. One (1) or more first-, second-, or third-degree relative on the same side of the family with **ANY** of the following:

a) Breast cancer diagnosed at age 50 years or younger;

b) Male breast cancer;

c) Ovarian cancer;

d) Pancreatic cancer;

e) Metastatic prostate cancer;

f) High-risk group prostate cancer; **or**

g) Very high-risk group prostate cancer;

ix. Three (3) 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 an affected first- or second- degree relative with **ANY** of the following (including those with breast cancer not meeting the above criteria):

a. Individuals with a greater than 5% probability of a BRCA 1/2 pathogenic variant

based on prior probability models (e.g., Tyrer-Cuzick lifetime risk, BRCAPro, CanRisk).

b. First- or second-degree relative diagnosed with breast cancer at age 50 years or younger;

c. First- or second-degree relative diagnosed with breast cancer at any age with **ANY** of the following specific features:

i. Triple negative breast cancer (ER-/PR-/HER2-);

ii. Multiple primary breast cancers (synchronous or metachronous);

iii. Lobular breast cancer with personal or family history of diffuse gastric cancer (see Policy Statement II.H);

iv. Male breast cancer;

v. Ashkenazi Jewish ancestry;

vi. One (1) or more first-, second-, or third-degree relative on the same side of the family with **ANY** of the following:

a) Breast cancer diagnosed at age 50 years or younger;

b) Male breast cancer;

c) Ovarian cancer;

d) Pancreatic cancer;

e) Prostate cancer (metastatic prostate cancer;

f) High-risk group prostate cancer; **or**

g) Very high-risk group prostate cancer);

vii. Three (3) 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.

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 ovarian cancer, including fallopian tube cancer or peritoneal cancer, at any age;

2. An individual with family history of cancer only (unaffected member) with **ONE** of the following:

a. One (1) or more first or second degree relative with 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 lifetime risk, 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 pancreatic cancer at any age; **or**
2. An individual with family history of cancer only (unaffected member) with a first degree relative diagnosed with pancreatic cancer at any age.

D. **Testing criteria for prostate cancer susceptibility genes** (Specifically ATM, BRCA1, BRCA2, CHEK2, HOXB13z, PALB2, and TP53):

1. An individual with a personal history of prostate cancer with **ANY** of the following specific features:
   a. Metastatic (stage IVB) or node-positive (stage IVA) prostate cancer; proven by biopsy and/or radiographic evidence which includes distant metastasis and regional bed or nodes and is not a biochemical recurrence;
   b. High-risk group;
   c. very-high-risk group prostate cancer; **or**
   d. Ashkenazi Jewish ancestry.
2. An individual with a personal history of prostate cancer, who does not meet the specific features listed above, **AND** a family history of cancer including:
   a. One (1) or more first-, second-, or third-degree relatives with **ANY** of the following:
      i. Breast cancer diagnosed at age 50 years or younger;
      ii. Male breast cancer at any age;
      iii. Ovarian cancer at any age;
      iv. Pancreatic cancer at any age; **or**
      v. 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;
   b. One (1) or more first-degree relative with prostate cancer at age 60 years or younger;
   c. Three (3) or more first-, second-, or third-degree relative prostate cancer (any grade) or breast cancer at any age, including the member with prostate cancer;
3. 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.

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;

b. An individual with a personal history of an LS-related cancer* and **ANY** of the following:

i. Diagnosed before 50 years of age;

ii. Diagnosed at any age with synchronous or metachronous LS-related cancer*;

iii. One (1) or more first- or second-degree relatives with an LS-related cancer* diagnosed before 50 years of age; **or**

iv. Two (2) or more first- or second-degree relatives with an LS-related cancer* diagnosed at any age;

c. An individual with a family history of **ANY** of the following:

i. One (1) or more first-degree relatives diagnosed with a colorectal or endometrial cancer before 50 years of age;

ii. One (1) or more first-degree relatives diagnosed with a colorectal or endometrial cancer and a synchronous or metachronous LS-related cancer* at any age;

iii. Two (2) 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 (3) or more first- or second-degree relatives with LS-related cancers* diagnosed at any age;

d. Individuals with a 5% or greater risk of having a mismatch repair (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 polymerase chain reaction (PCR), next-generation sequencing (NGS), or immunohistochemistry (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. **Mismatch repair (MMR) deficiency screening (via Microsatellite instability (MSI) testing, IHC, or NGS) of tumor tissue:**

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;

d. Tumor tissue of patients with multiple colon polyps, at least one (1) of which is an adenomatous polyp, and who meet **ANY** of the following Bethesda criteria:

i. Individual 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 or other 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 (1) or more first-degree relatives with colorectal cancer or Lynch syndrome-related cancer*, with one of the cancers diagnosed before age 50 years; **or**

v. Individuals with colorectal cancer and colorectal cancer diagnosed in two (2) 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 known APC pathogenic variant in the family. (Testing for the specific known familial pathogenic variant rather than full gene sequencing is recommended.);
   b. Individuals with personal history of **one (1) or more** of the following:
      i. 10 or more cumulative adenoma
      ii. desmoid tumor;
      iii. hepatoblastoma;
      iv. cribriform-morular variant of papillary thyroid cancer;
      v. multifocal/bilateral congenital hypertrophy of retinal pigment epithelium (CHRPE) or unilateral CHRPE; **or**
      vi. meets criteria for Serrated Polyposis Syndrome (SPS) including **EITHER** of the following:
         a) Five (5) or more lesions/polyps proximal to the rectum that are 5 mm in size with two (2) or more of these lesions/polyps 10 mm or greater with at least some adenomas; **or**
         b) More than 20 lesions/polyps of any size but distributed throughout the colon with five (5) or more being proximal to the rectum with at least some adenomas;
   c. Individuals with a family history of polyposis and family unwilling/unable to have testing.
4. **MUTYH- Associated Polyposis (MAP) (germline pathogenic variant of MUTYH):**
   a. Individuals with a personal history of **ANY** of the following:
      i. 10 or greater adenomas;
      ii. Five (5) or more lesions/polyps proximal to the rectum that are five mm in size with two (2) 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 (5) or more which are proximal to the rectum;
   b. Individuals with a family history including one (1) or more siblings with known MUTYH-associated polyposis; or
   c. 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 (2) or more** of the following:
      i. Two (2) or more Peutz-Jeghers-type hamartomatous polyps of the GI tract;
      ii. Mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers;
      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 (1) or more** of the following:
      i. Five (5) 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;
   b. In first-degree relatives (e.g., siblings, parents, offspring) of patients diagnosed with JPS;
   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):**
   1. Individuals with a family history of a known PTEN pathogenic or likely pathogenic variant; (Testing for the specific known familial mutation rather than full gene sequencing is recommended.)
   2. Individuals with a personal history of **ANY** of the following:
      a. Bannayan-Riley-Ruvalcaba syndrome (BRRS);
      b. Adult Lhermitte-Duclos disease (cerebellar tumors);
      c. Autism spectrum disorder and macrocephaly;
      d. Two (2) or more biopsy-proven trichilemmomas;
      e. Two (2) or more major criteria (one must be macrocephaly);

f. Three (3) major criteria, without macrocephaly;

g. One (1) major and three (3) or more minor criteria**; **or**

h. Four (4) or more minor criteria.

**If an individual has two (2) or more major criteria, such as breast cancer and non-medullary thyroid cancer, but does not have macrocephaly, then one (1) of the major criteria may be included as one (1) of the three (3) minor criteria to meet testing criteria.

3. 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 **EITHER** of the following diagnostic criteria:

   a. Any **ONE (1)** major criterion; **or**

   b. **Two** (2) minor criteria.

Major Criteria:	**Minor Criteria:**
i. Breast cancer; ii. Endometrial cancer; iii. Follicular thyroid cancer; iv. Multiple gastrointestinal (GI) hamartomas or ganglioneuromas; v. Lhermitte-Duclos disease (adult) vi. Macrocephaly (megalocephaly, i.e., 97% or greater, 58 cm in adult women, 60 cm in adult men); vii. Macular pigmentation of glans penis; viii. Mucocutaneous lesions (**ANY** of the following): a) One biopsy-proven trichilemmoma; b) Multiple palmoplantar keratosis (pits or acral hyperkeratotic papules; c) Oral papillomas (particularly on tongue and gingiva); d) Multiple mucocutaneous neuromas.	i. Autism spectrum disorder; ii. Colon cancer; iii. Esophageal glycogenic acanthosis (three or more); iv. Lipomas; v. Intellectual disability (i.e., IQ 75 or less); vi. Papillary or follicular variant of papillary thyroid cancer; vii. Thyroid structural lesions (e.g., adenoma, nodule(s), goiter); viii. Renal cell carcinoma; ix. Single GI hamartoma or ganglioneuroma; x. Testicular lipomatosis; xi. Vascular anomalies (including multiple intracranial developmental venous anomalies).

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

1. 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.)
2. Individual meeting Classic LFS criteria which includes **ALL** the following:
    a. Personal history of sarcoma diagnosed before age 45 years;
    b. One (1) first-degree relative diagnosed with cancer before age 45 years; **and**
    c. One (1) 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.
3. Individual meeting Chompret criteria which includes **ANY** of the following:
    a. 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 [ACC]) diagnosed before age 46 years; and **EITHER** of the following:
        i. at least one (1) 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**
        ii. at least one (1) first- or second-degree relative with multiple primaries diagnosed at any age;
    b. Individual with multiple tumors (except multiple breast tumors), two (2) of which belong to LFS tumor spectrum with the initial cancer diagnosed before age 46 years;
    c. Individual with adrenocortical carcinoma (ACC), or choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype diagnosed at any age, regardless of the family history; **or**
    d. 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.
4. Personal history or family history of pediatric hypodiploid acute lymphoblastic leukemia.

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

1. Family history (may include individual with personal history) of two (2) cases of gastric cancer in first- or second-degree relatives, at least one (1) of which is a confirmed diffuse gastric cancer diagnosed at any age;
2. Individual with a personal history of diffuse gastric cancer at any age;
3. 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;

4. Family history of two (2) cases of lobular breast cancer in first- or second-degree relatives before 50 years of age;
5. 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;
6. Personal history of bilateral lobular breast cancer; **or**
7. Individual with a family history of 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 pathogenic variants):**

1. Individuals with a personal history of apparently sporadic medullary thyroid carcinoma;
2. Individuals with a family history of a known RET pathogenic variants; **or**
3. Individuals with a family history of medullary thyroid carcinoma but not previously evaluated for RET pathogenic variants.

RELATED POLICIES

Corporate Medical Policy

2.02.03 Genetic Testing for Inherited Disorders

4.01.03 Prenatal Genetic Testing

11.01.03 Experimental or Investigational Services

POLICY GUIDELINE(S)

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 available.; and

D. Documentation of discussion between the provider (e.g., physician, genetic counselor, medical geneticist, oncologist, surgeon) 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. Available from: https://bcrisktool.cancer.gov/calculator.html [accessed 2026 Feb 20]

B. Carrier Estimation Algorithm (BOADICEA). Available from: http://ccge.medschl.cam.ac.uk/boadicea/ [accessed 2026 Feb 20]

C. Tyrer-Cuzick risk model, also known as the International Breast Cancer Intervention Study (IBIS) tool. Available from: https://magview.com/ibis-risk-calculator/ [accessed 2026 Feb 20]

D. PREMM5 Lynch Syndrome Prediction Model. Available from: https://premm.dfci.harvard.edu [accessed 2026 Feb 20]

*Each mutation probability model has its unique attributes determined by the methods, sample size, and population used to create it. Some models use 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 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

The National Comprehensive Cancer Network (NCCN) guidelines for ovarian cancer including fallopian tube cancer and primary peritoneal cancer (V.3.2025) 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

The NCCN guidelines for Prostate Cancer (V.5.2026) define 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, are included in the NCCN guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (V.2.2026). 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 cancer 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 guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (V.1.2025) recommend 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 individuals 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 individuals. 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

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);
- One of whom is a first-degree relative of the other two;
- HNPCC-associated cancer involving at least two generations;
- 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.

Revised Bethesda Guidelines

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;
- 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 LS-associated tumors* regardless of age;
- Individuals with colorectal cancer with the MSI-H histology who were diagnosed before age 60 years;
- 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 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. CS 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.

SUPPORTIVE LITERATURE

Coughlin et al (2022) published a retrospective, cohort study of adults with colorectal cancer (CRC) who underwent multigene panel testing (MGPT) of greater than 10 genes at a commercial laboratory between March 2015 and May 2021. All data were prospectively collected through a single commercial laboratory and retrospectively analyzed. A total of 34,244 individuals with a history of CRC underwent germline MPGT and were included in the analysis. This cohort was predominantly female (60.7%), White (70.6%), and age 50 years or older (68.9%), with 35.5% also reporting a non-colorectal malignancy. At least one pathogenic/likely pathogenic germline variant (PGV) was found in 4,864 (14.2%), with 3,111 (9.1%) having a PGV associated with increased CRC/polyposis risk and 1,048 (3.1%) having an otherwise clinically actionable PGV. Larger gene panels were not clearly associated with higher yield of clinically actionable PGVs. PGVs were more prevalent in individuals of Ashkenazi Jewish descent ($P < .001$) and Hispanic ethnicity ($P < .001$). Across all ages, panel sizes, and races/ethnicities, the rate of clinically actionable PGVs on MGPT was 7.9% or greater. A variant of uncertain significance was identified in 13,094 individuals (38.2%). The authors concluded the study demonstrated a high rate of clinically actionable variants detected across all age groups, panel sizes, and racial/ethnic groups and supports consideration of broadening germline genetic testing criteria for individuals with CRC. Limitations of the study include information used was from test requisition forms that were submitted by clinicians, and, therefore, confirmation of clinical information with the patients' primary medical record was not possible. Data included all individuals who had CRC even if CRC was not the primary reason for these patients to undergo genetic testing. Finally, the patients included in the cohort studied had MPGT ordered under recent guidelines requiring a diagnosis of CRC younger than age 50 years or other features known to bias for the presence of germline genetic drivers.

Whitworth et al (2022) sought to examine the implications of universal germline testing of patients with breast cancer with respect to clinical decision-making. Current NCCN guidelines recommend germline genetic testing for high-risk genes in selected patients with breast cancer. The clinical utility of recommending testing all patients with breast cancer with multigene panels is being considered. This retrospective study included 952 participants who were previously assessed as in criteria or out of criteria according to 2017 NCCN guidelines and underwent testing with a MGPT (80 genes)

between 2017 and 2018. Patients were women and men aged 18 to 90 years, with a new and/or previous diagnosis of breast cancer who had not undergone either single or multigene testing. Clinicians from 20 community and academic sites documented patient clinical information were asked to assess changes to clinical management as a result of germline genetic testing. Informative clinician-reported recommendations were provided for 939 (467 in-criteria and 472 out-of-criteria) of the patients with breast cancer (936 [99.7%] female; 702 [74.8%] White; mean [SD] age at initial diagnosis, 57.6 [11.5] years). One or more changes were reported for 31 of 37 (83.8%) in-criteria patients and 23 of 34 (67.6%) out-of-criteria patients with a pathogenic or likely pathogenic variant. Recommendations were changed as a result of testing results for 14 of 22 (63.6%) out-of-criteria patients who had a variant in a breast cancer predisposition gene. Clinicians considered testing beneficial for two-thirds of patients with pathogenic or likely pathogenic variants and for one-third of patients with either negative results or variants of uncertain significance. There was no difference in variant rate between patients meeting the BRCAPRO threshold (≥10%) and those who did not (P = .86, Fisher exact test). No changes to clinical recommendations were made for most patients with negative results (345 of 349 patients [98.9%]) or variants of uncertain significance (492 of 509 patients [96.7%]). The authors concluded that the study showed universal germline testing informs clinical decision-making and provides access to targeted treatments and clinical trials for all patients with breast cancer. Limitations were noted to include the study sites selected were primarily breast surgery practices; thus, the patients studied were biased toward those with early-stage resectable disease. The study was performed before NCCN guidelines were updated to screen patients for PARP inhibitor treatment eligibility. The out of criteria patient representation is necessarily skewed to patients older than age 45 years, as determined by the NCCN guidelines; however, prevalence of PGVs in high-penetrance genes has been shown to be significant in women aged 60 to 65 years. Lastly, patients were not studied longitudinally to determine longer-term outcomes such as progression-free survival.

Samadder et al (2021) examined the prevalence of pathogenic germline variants (PGVs) in patients with cancer using a universal testing approach compared with targeted testing based on clinical guidelines and the uptake of cascade family variant testing (FVT). This prospective, multicenter cohort study assessed germline genetic alterations among patients with solid tumor cancer receiving care at Mayo Clinic cancer centers and a community practice between April 1, 2018, and March 31, 2020. Patients were not selected based on cancer type, disease stage, family history of cancer, ethnicity, or age. Germline sequencing was completed using a greater than 80-gene next-generation sequencing platform. A total of 2984 patients (mean [SD] age, 61.4 [12.2] years; 1582 [53.0%] male) were studied. Pathogenic germline variants were found in 397 patients (13.3%), including 282 moderate- and high-penetrance cancer susceptibility genes. Variants of uncertain significance were found in 1415 patients (47.4%). A total of 192 patients (6.4%) had incremental clinically actionable findings that would not have been detected by phenotype or family history-based testing criteria. Of those with a high-penetrance PGV, 42 patients (28.2%) had modifications in their treatment based on the finding. Only younger age of diagnosis was associated with presence of PGV. Only 70 patients (17.6%) with PGVs had family members undergoing no-cost cascade FVT. The authors found that universal multigene panel testing among patients with solid tumor cancer was associated with an increased detection of heritable variants over the predicted yield of targeted testing based on

guidelines. Nearly 30% of patients with high-penetrance variants had modifications in their treatment. Uptake of cascade FVT was low despite being offered at no cost. Limitations include a lack of long-term follow-up to assess cancer-related mortality and the morbidity associated with targeted therapy, preventive screening, or prophylactic surgery. The interpretation of family history and need for testing was performed by expert reviewers using guidelines that changed during the study. The cascade FVT portion of the study relied on communication of genetic test results to family members solely by proband-mediated disclosure, which is complicated by a range of complex personal, social, and cultural factors.

PROFESSIONAL GUIDELINE(S)

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 individuals 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.

<u>Breast Cancer</u>

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.

The NCCN guidelines for Breast Cancer (V.1.2026) recommend assessing for germline BRCA1/2 mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy. The guidelines state that 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 (Manahan 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

The NCCN guidelines for ovarian cancer including fallopian tube cancer and primary peritoneal cancer (V.3.2025) 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.

American Society of Clinical Oncology (ASCO) Guidelines for epithelial ovarian cancer (Konstantinopoulos 2020) recommend all women diagnosed with epithelial ovarian cancer should have germline genetic testing for BRCA1/2 and other ovarian cancer susceptibility genes. In women who do not carry a germline pathogenic or likely pathogenic BRCA1/2 variant, somatic tumor testing

for BRCA1/2 pathogenic or likely pathogenic variants should be performed. Women with identified germline or somatic pathogenic or likely pathogenic variants in BRCA1/2 genes should be offered treatments that are US Food and Drug Administration (FDA) approved in the upfront and the recurrent setting. Women diagnosed with clear cell, endometrioid, or mucinous ovarian cancer should be offered somatic tumor testing for mismatch repair deficiency (dMMR). Women with identified dMMR should be offered FDA-approved treatment based on these results. Genetic evaluations should be conducted in conjunction with health care providers familiar with the diagnosis and management of hereditary cancer. First- or second-degree blood relatives of a patient with ovarian cancer with a known germline pathogenic cancer susceptibility gene variant should be offered individualized genetic risk evaluation, counseling, and genetic testing. Clinical decision making should not be made based on a variant of uncertain significance. Women with epithelial ovarian cancer should have testing at the time of diagnosis.

Prostate Cancer

The NCCN guidelines for prostate cancer (V.5.2026) 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

The NCCN guidelines for pancreatic adenocarcinoma (V.2.2025) 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.

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 the 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, Endometrial, and Gastric (V.1.2025) 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

The International Cowden Consortium criteria for Cowden syndrome have been updated several times since 1996 and are the basis for the NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (V.1.2025) 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, ovarian, pancreatic, and prostate (V.2.2026) cancers utilize both the classic Li Fraumeni clinical criteria and the Chompret criteria when recommending genetic testing for a mutation in the TP53 gene. 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 Guidelines Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (V.1.2025) 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.

The NCCN guidelines for Thyroid Carcinoma (V.1.2025) 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.

The NCCN guidelines continue to address other thyroid carcinomas. They state follicular thyroid cancer is a feature of some inherited cancer syndromes associated with significant clinical implications for the patient and relatives. The most common of these is Cowden Syndrome (CS)/PTEN Hamartoma Tumor Syndrome (PHTS). PHTS should be suspected if the patient also has a personal or family history of breast cancer, endometrial cancer, colorectal cancer/colorectal hamartomas, multiple mucocutaneous lesions, macrocephaly, and/or a wide range of other features as detailed in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. All patients who meet these criteria for PHTS should receive genetic risk assessment, counseling, and testing. Other patients with two or more first-degree relatives who have also had non-medullary thyroid cancer, or who have a personal or family history of multiple other cancers, may be candidates for genetic testing for germline mutations in other hereditary cancer genes.

Multigene Panel Testing

The NCCN guidelines on Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (V2.2026) 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.

These NCCN guidelines 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 increases. 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. However, multigene panel testing is often indicated in these individuals if family history suggests a different syndrome in addition to the known variant. In individuals from a family without a known P/LP variant, germline multigene testing is recommended for those individuals who meet the testing criteria.

The NCCN guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (V.1.2025) state 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 of 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.

ASCO guidelines for the selection of germline genetic testing panels in patients with cancer (Tung 2024) aim to guide the use of multigene panels. The ASCO Expert Panel recommended the following: Patients should have a family history taken and recorded that includes details of cancers in first- and second-degree relatives and the patient's ethnicity. When more than one gene is relevant based on personal and/or family history, multigene panel testing should be offered. When considering what genes to include in the panel, the minimal panel should include the more strongly recommended genes from the table below and may include those less strongly recommended. A broader panel may be ordered when the potential benefits are clearly identified, and the potential harm from uncertain results should be mitigated. Patients who meet criteria for germline genetic testing should be offered germline testing regardless of results from tumor testing. Patients who would not normally be offered germline genetic testing based on personal and/or family history criteria but who have a pathogenic or likely pathogenic variant identified by tumor testing in a gene BRCA1, BRCA2, BRIP1, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, RAD51C, RAD51D, RET, SDHAF2, SDHB, SDHC, SDHD, TMEM127, TSC2, VHL should be offered germline testing. If the patient is 30 years or younger, testing should be offered if a variant is found in APC, PTEN, RB1, or TP53 genes.

Cancer Type and Specific Population	More Strongly Recommended (higher relative risk of cancer or highly actionable)	Less Strongly Recommended (moderate relative risk of cancer or potential impact for therapy/ change in medical management)
Breast Cancer	BRCA1, BRCA2, PALB2 CDH1, PTEN, STK11, TP53	ATM, BARD1, CHEK2, RAD51C, RAD51D NF1
Colorectal cancer	APC, EPCAM, MLH1, MSH2, MSH6, MUTYH, NTHL1, PMS2, POLD1, POLE, BMPR1A, SMAD4, STK11, TP53	AXIN2, CHEK2, MBD4 GREM1, MSH3, PTEN, RNF43
Endometrial cancer	EPCAM, MLH1, MSH2, MSH6, PMS2, PTEN, STK11	NA
Gastric cancer	APC, CTNNA1, EPCAM, MLH1, MSH2, MSH6, PMS2, BMPR1A, CDH1, SMAD4, STK11	NA
Gastrointestinal stromal tumors	KIT, PDGFRA If SDH-deficient or SDH-mutant tumor: SDHA, SDHAF2, SDHB, SDHC, SDHD If NF1-mutated tumor: NF1	If tumor is not SDH-deficient, SDH-mutated, or NF1-mutated: NF1, SDHA, SDHAF2, SDHB, SDHC, SDHD
Medullary thyroid carcinoma	RET	NA

Non–small cell lung cancer—if EGFR tumor pathogenic variant (such as p.T790M) found with no previous EGFR-TKI therapy	EGFR, STK11	TP53
Adrenocortical tumors	APC, EPCAM, MEN1, MLH1, MSH2, MSH6, PMS2, TP53	NA
Melanoma, cutaneous	CDKN2A, CDK4	BAP1, MC1R, MITF, POT1, TERT, PTEN
Melanoma, uveal	BAP1	NA
Ovarian cancer (epithelial)	BRCA1, BRCA2, BRIP1, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, RAD51C, RAD51D	ATM
Pancreatic adenocarcinoma	ATM, BRCA1, BRCA2, CDK4, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, TP53	APC
Phaeochromocytomas and paragangliomas	FH, MAX, RET, SDHA, SDHB, SDHC, SDHD, TMEM127, NF1, VHL	EGLN1, EPAS1, KIF1B, MET, SDHAF2
Prostate cancer	BRCA1, BRCA2, EPCAM, HOXB13, MLH1, MSH2, MSH6, PMS2	ATM, CHEK2, PALB2
Renal cell carcinoma	BAP1, FH, FLCN, MET, SDHA, SDHAF2, SDHB, SDHC, SDHD, PTEN, VHL	TSC1, TSC2
Sarcoma (soft tissue or osteosarcoma)	TP53	NF1, RB1

Testing Unaffected Family Members

The NCCN guidelines for genetic/familial high-risk assessment of breast, ovarian, pancreatic, and prostate (V.2.2026) and guidelines for genetic/familial high-risk assessment of colorectal, endometrial, and gastric (V1.2025) updated recommendations regarding unaffected family members in the absence of a known familial pathogenic or likely pathogenic variant. They now state that while testing an affected family member is most informative, it is also appropriate to test unaffected family members who meet testing criteria. They no longer recommend attempting, if possible, to test the family member with highest likelihood of a pathogenic or likely pathogenic variant before testing an unaffected family member. A negative test result in such cases, however, is considered indeterminate

and does not provide the same level of information as when there is a known pathogenic or likely pathogenic variant in the family. Thus, one should be mindful that, when testing unaffected individuals (in the absence of having tested affected family members), significant limitations may exist in interpreting the test results and testing multiple family members may be indicated since absence of a pathogenic or likely pathogenic variant in one unaffected relative does not rule out a pathogenic or likely pathogenic variant in other family members.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as laboratory service. Laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests must be licensed by CLIA for high-complexity testing. More information is available at: Clinical Laboratory Improvement Amendments (CLIA) | FDA [accessed 2026 Feb 20]

CODE(S)

- Codes may not be covered under all circumstances.
- Code list may not be all inclusive (AMA and CMS code updates may occur more frequently than policy updates).
- (E/I)=Experimental/Investigational
- (NMN)=Not medically necessary/appropriate

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)

Code	Description
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
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

Code	Description
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) (e.g., breast and pancreatic cancer) gene analysis; full gene sequence
81308	PALB2 (partner and localizer of BRCA2) (e.g., 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
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)

Code	Description
81353	TP53 (Tumor Protein 53) (e.g., Li-Fraumeni syndrome) gene analysis; known familial variant
81401	Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
81402	Molecular pathology procedure, Level 3 (e.g., >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])
81403	Molecular pathology procedure, Level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
81404	Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
81405	Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81406	Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
81407	Molecular pathology procedure, Level 8 (e.g., analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
81408	Molecular pathology procedure, Level 9 (e.g., analysis of >50 exons in a single gene by DNA sequence analysis)
81432	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer, hereditary pancreatic cancer, hereditary prostate cancer), genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants
81435	Hereditary colon cancer-related disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants

Code	Description
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)
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)
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)

Code	Description
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 81407) (RNAinsight for PALB2, Ambry Genetics)
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)

Code	Description
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)
0474U	Hereditary pan-cancer (e.g., hereditary sarcomas, hereditary endocrine tumors, hereditary neuroendocrine tumors, hereditary cutaneous melanoma), genomic sequence analysis panel of 88 genes with 20 duplications/deletions using next-generation sequencing (NGS), Sanger sequencing, blood or saliva, reported as positive or negative for germline variants, each gene (GeneticsNow Comprehensive Germline Panel, GoPath Diagnostics, Inc)
0475U	Hereditary prostate cancer-related disorders, genomic sequence analysis panel using next-generation sequencing (NGS), Sanger sequencing, multiplex ligation-dependent probe amplification (MLPA), and array comparative genomic hybridization (CGH), evaluation of 23 genes and duplications/deletions when indicated, pathologic mutations reported with a genetic risk score for prostate cancer (ProstateNow Prostate Germline Panel, GoPath Diagnostics, 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)
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

Code	Description
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

Code	Description
Z80.42	Family history of malignant neoplasm of prostate
Z80.8	Family history of malignant neoplasm of other organs or systems
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

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SEARCH TERMS

Not Applicable

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

LCD - Molecular Pathology Procedures (L35000) [accessed 2026 Feb 20]

Article - Billing and Coding: Molecular Pathology Procedures (A56199) [accessed 2026 Feb 20]

NCD - Next Generation Sequencing (NGS) (90.2) [accessed 2026 Feb 20]

PRODUCT DISCLAIMER

- Services are contract dependent; if a product does not cover a service, medical policy criteria do not apply.

- If a commercial product (including an Essential Plan or Child Health Plus product) covers a specific service, 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 HISTORY/REVISION	
Committee Approval Dates	
12/21/23, 04/18/24, 04/17/25, 04/16/26	
Date	**Summary of Changes**
04/16/26	• Annual update, policy intent unchanged.
04/17/25	• Annual update, policy statement I.E updated to include all unaffected family members who meet specific testing criteria
01/01/25	• Summary of changes tracking implemented.
12/21/23	• Original effective date