Genetic Testing for Hereditary Cancer

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➲ Instructions for Use

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Related Commercial/Individual Exchange Policy
- Preventive Care Services

Community Plan Policy
- Genetic Testing for Hereditary Cancer

Medicare Advantage Policy
- Molecular Pathology/Molecular Diagnostics/ Genetic Testing

Application

UnitedHealthcare Commercial
This Medical Policy applies to UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange
This Medical Policy applies to Individual Exchange benefit plans.

Coverage Rationale

Pretest genetic counseling is strongly recommended to inform persons being tested about the advantages and limitations of the test, as applied to a unique person.

Single-gene testing and known mutation testing for familial cancer are proven and medically necessary.

Individuals With a Personal History of a Primary Solid Tumor
***BRCA1/2* gene testing is proven and medically necessary for individuals with a personal history of Breast Cancer diagnosed at age 65 years or younger.**

Genetic testing with a Multigene hereditary cancer Panel for individuals with a personal history of a Primary Solid Tumor (excluding basal or squamous cell skin cancer) is proven and medically necessary when at least one of the following criteria is met:
- Individual has a personal history of at least one of the following:
  - Breast Cancer diagnosed at age 50 years or younger
  - Metastatic Breast Cancer
  - Multiple primary Breast Cancers (as a prior diagnosis or as a bilateral primary cancer)
  - Triple-Negative Breast Cancer
  - Lobular Breast Cancer and a personal or family history of diffuse gastric cancer
  - Breast Cancer and Ashkenazi Jewish ancestry
  - Breast Cancer and individual was assigned male at birth
  - Breast Cancer and unknown or Limited Family History
  - Breast Cancer or prostate cancer and at least one first- or second-degree relative with a BRCA-Related Cancer

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- Ovarian Cancer (including fallopian tube cancer, primary peritoneal cancer, sex-cord tumors with annular tubules, and/or hypercalcemic-type small cell carcinoma of the ovary)
- Serous tubal intraepithelial carcinoma
- Pancreatic cancer
- Metastatic prostate cancer
- Lynch Syndrome-Associated Cancer
- Neuroendocrine tumor (e.g., adrenocortical carcinoma, paraganglioma, pheochromocytoma)
- Malignant phyllodes tumors
- Renal cell carcinoma and any of the following:
  - Diagnosed at 46 years of age or younger
  - Diagnosed at any age with bilateral or multifocal tumors
  - Has one or more first- or second-degree relatives with renal cell carcinoma
  - Has a personal or family history of mesothelioma or uveal melanoma
- At least two different Primary Solid Tumors (excluding basal or squamous cell skin cancer)

or

- Individual has a personal history of a Primary Solid Tumor (excluding basal or squamous cell skin cancer) and a family history of cancer, which includes at least one of the following:
  - At least one Close Blood Relative with a history of a Lynch Syndrome-Associated Cancer
  - At least one Close Blood Relative diagnosed with a Primary Solid Tumor (excluding basal or squamous cell skin cancer) at age 40 years or younger
  - At least two Close Blood Relatives (in addition to affected individual) on the same side of the family diagnosed with any Primary Solid Tumor (excluding basal or squamous cell skin cancer)

or

- Individual has a personal history of a Primary Solid Tumor (excluding basal or squamous cell skin cancer) and at least one of the following:
  - A pathogenic variant was detected in tumor tissue that has clinical implications if detected in the germline (e.g., *BRCA1, BRCA2, BRIP1, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, RAD51C, RAD51D, RET, SDHAF2, SDHB, SDHC, SDHD, TMEM127, TSC2, VHL APC, PTEN, RB1, TP53*)
  - Tumor tissue testing demonstrated that the cancer was microsatellite instability high or had immunohistochemical staining showing the absence of one or more mismatch repair proteins (*MLH1, MSH2, MSH6,* or *PMS2*)
  - Individual has renal cell carcinoma and tumors have the following histological characteristics:
    - Multifocal papillary histology
    - Hereditary leiomyomatosis and renal cell cancer-associated renal cell carcinoma, renal cell carcinoma with fumarate hydratase deficiency or other histological features associated with hereditary leiomyomatosis and renal cell cancer
    - Birt-Hogg-Dubé syndrome–related histology
    - Angiomyolipomas of the kidney and one additional tuberous sclerosis complex criterion in the same individual
    - Succinate dehydrogenase–deficient renal cell carcinoma histology
  - Individual has a Tyrer-Cuzick, BRCAPRO, or CanRisk score of 2.5% or greater for a *BRCA1/2* pathogenic variant
  - Individual has a PREMM$_5$, MMRpro, or MMRpredict score of 2.5% or greater for having a Lynch syndrome gene mutation

Individuals With No Personal History of a Primary Solid Tumor

Genetic testing with a Multigene hereditary cancer Panel or testing of *BRCA1/2* for individuals with no personal history of a Primary Solid Tumor (excluding basal or squamous cell skin cancer) is proven and medically necessary if at least one of the following criteria is met:

- At least one first-degree relative with a history of at least one of the following:
  - Two or more different Primary Solid Tumors (excluding basal or squamous cell skin cancer)
  - Lynch Syndrome-Associated Cancer
  - Neuroendocrine tumor (e.g., adrenocortical carcinoma, paraganglioma, pheochromocytoma)

or

- At least one first- or second-degree relative with a history of at least one of the following:
  - Breast Cancer diagnosed at age 50 years or younger
  - Triple-Negative Breast Cancer
  - Breast Cancer and relative was assigned male at birth
  - Metastatic prostate cancer
  - Ovarian Cancer (including fallopian tube cancer and/or primary peritoneal cancer)
  - Pancreatic cancer

or

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- At least one second-degree relative with a history of at least one of the following:
  - Two or more Lynch Syndrome-Associated Cancers
  - Lynch Syndrome-Associated Cancer diagnosed at age 50 years or younger

  or
- Family history includes at least one of the following:
  - Two or more second-degree relatives on the same side of the family with a Lynch Syndrome-Associated Cancer
  - Two or more first- or second-degree relatives on the same side of the family with renal cell carcinoma
  - At least three Close Blood Relatives on the same side of the family diagnosed with any Primary Solid Tumor (excluding basal or squamous cell skin cancer)
  - Ashkenazi Jewish ancestry and at least one Close Blood Relative with a BRCA-Related Cancer
  - Family member who meets diagnostic criteria (personal history of at least 10 cumulative adenomas) for a polyposis syndrome and affected family member(s) is unwilling/unable to have genetic testing
  - First-degree relative meeting criteria for genetic evaluation for renal cell carcinoma but is unwilling/unable to have genetic testing

  or
- A personal history of colorectal polyposis with at least 10 adenomas; or
- Any of the following:
  - Individual has a Tyrer-Cuzick, BRCAPRO, or CanRisk score of 5% or greater for a *BRCA1/2* pathogenic variant; or
  - Individual has a PREMM$_5$, MMRpro, or MMRpredict score of 5% or greater for having a Lynch syndrome gene mutation

Genetic testing with a Multigene hereditary cancer Panel for individuals diagnosed with cancer at age 18 years or younger is proven and medically necessary.

Multigene hereditary cancer Panels are unproven and not medically necessary for all other indications.

RNA panel testing for hereditary cancers is unproven and not medically necessary for all indications.

Genetic testing for the purpose of polygenic risk scoring for hereditary cancers is unproven and not medically necessary for all indications.

Whole-exome and whole-genome sequencing for the purpose of identifying hereditary cancer syndromes or hereditary cancer syndrome risk is unproven and not medically necessary.

Medical Records Documentation Used for Reviews

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. Medical records documentation may be required to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the service requested; refer to the guidelines titled Medical Records Documentation Used for Reviews.

Definitions

Age Guidelines: For the statements that include Age Guidelines, a person is considered 45 years of age up until the day before their 46th birthday, and a person is considered 50 years of age up until the day before their 51st birthday.

***BRCA*-Related Cancers**: Breast Cancer, Ovarian Cancer/fallopian tube cancer/primary peritoneal cancer, pancreatic adenocarcinoma, and prostate cancer [National Comprehensive Cancer Network (NCCN), Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate v1.2026].

Breast Cancer: Either invasive carcinomas or noninvasive (in situ) ductal carcinoma types (NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate v1.2026).

Close Blood Relatives: Defined as follows (NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate v1.2026):
- First-degree relatives include parents, siblings, and offspring
- Second-degree relatives include half-brothers/-sisters, aunts/uncles, grandparents, grandchildren, and nieces/nephews affected on the same side of the family

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- Third-degree relatives include first cousins, great-aunts/-uncles, great-grandchildren, and great-grandparents affected on the same side of the family

Founder Mutation: A gene mutation observed with high frequency in a group that is or was geographically or culturally isolated, in which one or more of the ancestors was a carrier of the mutant gene. This phenomenon is often called a Founder effect [National Cancer Institute (NCI) Dictionary of Genetics Terms, 2025; NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate v1.2026].

Gleason Scoring: Gleason Scoring is a system of grading prostate cancer tissue based on how it looks under a microscope. Gleason Scores range from 2 to 10 and indicate how likely it is that a tumor will spread. A low Gleason Score means that the cancer tissue is similar to normal prostate tissue, and the tumor is less likely to spread. A high Gleason Score means that the cancer tissue is very different from normal, and the tumor is more likely to spread (NCI Dictionary of Cancer Terms, 2025).

Limited Family History: Fewer than two known first-degree or second-degree female relatives surviving beyond 45 years of age on either or both sides of the family (i.e., individual who is adopted) (NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate v1.2026).

Lynch Syndrome-Associated Cancer: Colorectal, endometrial, gastric, Ovarian, pancreatic, urothelial, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas, as seen in Muir-Torre syndrome (NCCN, Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric v1.2025).

Multigene Panel: Genetic tests that use next-generation sequencing to test multiple genes simultaneously. Also called multigene test, multiple-gene panel test, and multiple-gene test (NCI Dictionary of Genetics Terms, 2025). For the purposes of this policy, a Multigene Panel consists of five or more genes.

Ovarian Cancer: Includes fallopian tube cancers, primary peritoneal cancers, sex-cord tumors with annular tubules, and hypercalcemic-type small cell carcinoma of the ovary as well as epithelial or nonepithelial Ovarian Cancer (NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate v1.2026).

Personal and Family History Documentation: In the form of a pedigree drawing/diagram using standardized nomenclature, this should be in the contemporaneous medical records submitted with the testing request (i.e., request form) (NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate v1.2026).

$PREMM_5$: PREdiction Model for gene Mutations. The $PREMM_5$ model estimates the overall cumulative probability of having an *MLH1, MSH2, MSH6, PMS2*, or *EPCAM* gene mutation. Mutations in these genes are related to Lynch Syndrome (Kastrinos et al., 2017).

Primary Solid Tumor: An abnormal mass of tissue, typically not containing any cysts or liquid component, which is the original or first tumor that grew in the body. Cancer cells from a Primary Solid Tumor may spread to other parts of the body, forming new or secondary tumors that are the same kind of cancer as the primary tumor (NCI Dictionary of Cancer Terms, 2025).

Triple-Negative Breast Cancer: Refers to any Breast Cancer tumors that do not have estrogen receptors (ER), progesterone receptors (PR), or human epidermal growth factor receptor 2 (HER2) (NCI Dictionary of Cancer Terms, 2025; NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate v1.2026).

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other policies and guidelines may apply.

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CPT Code	Description
BRCA1* and *BRCA2	
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)
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)
Multigene Panel	
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])
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])
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])
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)
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)
0133U	Hereditary prostate cancer-related disorders, targeted mRNA sequence analysis panel (11 genes) (List separately in addition to code for primary procedure)
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)
0162U	Hereditary colon cancer (Lynch syndrome), targeted mRNA sequence analysis panel (MLH1, MSH2, MSH6, PMS2) (List separately in addition to code for primary procedure)
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
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
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

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CPT Code	Description
Multigene Panel	
0495U	Oncology (prostate), analysis of circulating plasma proteins (tPSA, fPSA, KLK2, PSP94, and GDF15), germline polygenic risk score (60 variants), clinical information (age, family history of prostate cancer, prior negative prostate biopsy), algorithm reported as risk of likelihood of detecting clinically significant prostate cancer
0651U	Oncology (hereditary cancer), genomic DNA, 55 hereditary cancer pre-dispositioned genes, next-generation sequencing (NGS) and digital multiplex ligation-dependent probe amplification for variants, small indels (<40 base pairs), using saliva, whole blood or nail clipping, interpretive clinical report with variant classification
0678U	Oncology (hereditary cancer), genome sequence for 117 genes (single-nucleotide variants, deletions/insertions, and characterized intronic variants), copy number variants, duplications/deletions, mobile element insertions and inversions, blood, saliva, cultured skin fibroblasts (skin biopsy) or extracted genomic DNA, diagnostic, identification and categorization of genetic variants
0679U	Oncology (hereditary hematologic cancer), genomic DNA, whole genome sequence (single-nucleotide variants, deletions/insertions, and characterized intronic variants), copy number variants, duplications/deletions, mobile element insertions and inversions, analysis of over 105 genes, genomic DNA isolated from blood, saliva, cultured skin fibroblasts (skin biopsy), identification and categorization of genetic variants
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
81437	Hereditary neuroendocrine tumor-related disorders (e.g., medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma), genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants
81441	Inherited bone marrow failure syndromes (IBMFS) (e.g., Fanconi anemia, dyskeratosis congenita, Diamond-Blackfan anemia, Shwachman-Diamond syndrome, GATA2 deficiency syndrome, congenital amegakaryocytic thrombocytopenia) sequence analysis panel, must include sequencing of at least 30 genes, including BRCA2, BRIP1, DKC1, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, GATA1, GATA2, MPL, NHP2, NOP10, PALB2, RAD51C, RPL11, RPL35A, RPL5, RPS10, RPS19, RPS24, RPS26, RPS7, SBDS, TERT, and TINF2
81479	Unlisted molecular pathology procedure
Whole Exome and Whole Genome Sequencing	
0212U	Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband
0213U	Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator genome (e.g., parent, sibling)
0214U	Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband
0215U	Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator exome (e.g., parent, sibling)

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CPT Code	Description
Whole Exome and Whole Genome Sequencing	
0265U	Rare constitutional and other heritable disorders, whole genome and mitochondrial DNA sequence analysis, blood, frozen and formalin-fixed paraffin-embedded (FFPE) tissue, saliva, buccal swabs or cell lines, identification of single nucleotide and copy number variants
0266U	Unexplained constitutional or other heritable disorders or syndromes, tissue-specific gene expression by whole-transcriptome and next-generation sequencing, blood, formalin-fixed paraffin-embedded (FFPE) tissue or fresh frozen tissue, reported as presence or absence of splicing or expression change
81415	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis
81416	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (e.g., parents, siblings) (List separately in addition to code for primary procedure)
81417	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (e.g., updated knowledge or unrelated condition/syndrome)
81425	Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis
81426	Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator genome (e.g., parents, siblings) (List separately in addition to code for primary procedure)
81427	Genome (e.g., unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (e.g., updated knowledge or unrelated condition/syndrome)

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Description of Services

Genetic testing for hereditary cancer susceptibility is used to predict an individual's risk of cancer development in the future. It has been estimated that 5% to 10% of all cancers are hereditary (Heald et al., 2016). Hereditary cancers typically have an earlier age at onset and have an autosomal dominant pattern of inheritance observable in a family (NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate v1.2026).

To identify whether an individual has an increased risk of having a hereditary cancer, it is important to take a detailed family history that includes first-, second-, and third-degree relatives and focuses on cancer diagnoses by age at onset, primary site(s), presence of bilateral disease, and current age or age at time of death. Other conditions that can be a feature of hereditary cancers should be noted as well as medical and surgical history. The individual should have a thorough physical examination performed by a clinician with familiarity with hereditary cancer syndromes. When applicable, risk assessment tools should be used to help identify the risk of an individual having a hereditary cancer gene. Some examples of tools include BRCAPRO, the Breast and Ovarian Cancer Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA), and PREMMplus (NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate v1.2026). Genetic testing is generally recommended when (1) there is a personal or family history consistent with hereditary cancer susceptibility, (2) the test can be adequately interpreted, and (3) the results can be used to diagnose or influence the medical management of the individual or at-risk family members (Robson et al., 2015).

Breast Cancer is the second most common cause of cancer-related death among women (Siegel et al., 2022), affecting approximately 13% of women in the general population at some time in their lives (National Cancer Institute, 2024). *BRCA1* and *BRCA2* genes, sometimes called tumor suppressor genes, can contain certain pathogenic changes that may lead to cancer development. Individuals who inherit harmful variants in one or both these genes are at an increased risk of Breast Cancer as well as several other types of cancer. Women who are found to have a harmful *BRCA* variant are significantly more likely to develop Breast or Ovarian Cancer in their lifetime; for Breast Cancer, the estimated risk is 60% to 72% for women who are carriers of a pathogenic/likely pathogenic (P/LP) *BRCA1* variant and 55% to 69% for *BRCA2* P/LP variant carriers. For Ovarian Cancer, cumulative risk (by age 70 years) associated with *BRCA1* P/LP variants is approximately 48.3%, and for *BRCA2*, the associated cumulative risk is approximately 20%. Breast and Ovarian Cancer are most notable, but an elevated risk of other cancers, including fallopian tube cancer, primary peritoneal cancer, prostate cancer, and pancreatic cancer, is also present. Other genes, such as *CDH1, PALB2, PTEN, STK11*, *ATM*, *BRIP1,* and *TP53*, have been linked to a higher risk of Breast, Ovarian, prostate, and/or pancreatic Cancer as well (National Cancer Institute, 2024; NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate v1.2026).

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The NCCN suggests that several specific genes may contribute to hereditary cancers, including but not limited to those in the table below (NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate v1.2026; NCCN, Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric v1.2025; NCCN, Prostate Cancer v2.2026).

Hereditary Cancer Type(s)	Associated Gene(s) (Not All Inclusive)
Breast Cancer	*BRCA1*, *BRCA2*, *CDH1*, *PALB2*, *PTEN*, *STK11*, and *TP53*
Ovarian Cancer	*ATM*, *BRCA1, BRCA2*, *BRIP1*, *PALB2*, *RAD51C*, *RAD51D*, *MLH1*, *MSH2*, *MSH6*, and *EPCAM*
Colon cancer/polyposis	*APC*, *MUTYH*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, *BMPR1A*, *SMAD4*, *PTEN, STK11,* and *TP53*
Pancreatic cancer	*ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, *STK11*, and *TP53*
Prostate cancer	*ATM*, *BRCA1*, *BRCA2*, *CHEK2*, *HOXB13, PALB2, and TP53*

Many Multigene hereditary cancer Panels are marketed commercially, most of which also include large deletion/duplication analysis. These Panels are intuitively attractive because they can rapidly test for numerous mutations related to increased cancer risk, both in a single gene and across multiple genes. It is also possible that these Multigene tests can, in the case of families in which more than one hereditary cancer syndrome is suspected, be performed more cost effectively than stepwise individual gene testing. However, many Panel tests also include low- to moderate-risk genes that may result in the identification of gene mutations that are of unclear clinical significance and/or cannot be used to direct an individual's medical management. Identification of mutations for which the clinical management is uncertain may lead to unnecessary follow-up testing and procedures, all of which have their own inherent risks [NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate v1.2026; NCCN, Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric v1.2025; LaDuca et al., 2014; Robson et al., 2015; Kurian et al., 2014 (included in Hayes, 2023); Tung et al., 2015; Plon et al., 2011].

Clinical Evidence

BRCA1/BRCA2

de Moraes et al. (2025) published the results of a comprehensive systematic review and meta-analysis that evaluated the association between *BRCA1/2* mutations and gastric cancer risk. Recent studies have implicated *BRCA1* and *BRCA2* gene mutations in increased gastric cancer susceptibility; this investigation aimed to better quantify the risk of gastric cancer in *BRCA1/2* mutation carriers and assess the frequency of *BRCA1/2* mutations in individuals who were already diagnosed with gastric cancer. The authors identified 14 studies that included over 160,000 individuals, 25,934 of whom were *BRCA1/2* mutation carriers. Pooled risk ratios (RRs) were then calculated, and heterogeneity was assessed using I^2 statistics. The analysis revealed that *BRCA1/2* mutations were significantly associated with an increased risk of gastric cancer (RR, 2.30; 95% CI, 1.33-3.97; $p = 0.003$; $I^2 = 82\%$ and RR, 2.45; 95% CI, 1.82-3.28; $p < 0.001$; $I^2 = 25\%$, respectively). Among the individuals who were diagnosed with gastric cancer, *BRCA1* mutation carriers had an RR of 3.02 ($p = 0.101$; $I^2 = 65\%$), and *BRCA2* carriers had an RR of 4.86 ($p < 0.001$; $I^2 = 0\%$). The authors proposed that these results suggest a significant association between *BRCA1/2* mutations and increased gastric cancer risk, particularly for *BRCA2*. They encouraged further research to validate these results, with the end goal of providing more data to inform risk management strategies for mutation carriers. Noted limitations include high heterogeneity, particularly in *BRCA1*-related analyses, which may impact the reliability of estimates. In addition, some of the comparisons lacked sufficient control data, and there was an overall lack of prospective data. There were no survival data related to the presence or lack of *BRCA* mutations, which may limit the understanding of the true impact of these genes in gastric cancer. Lastly, no data regarding Helicobacter pylori infection were included in the studies, which prevented investigation of potential interactions between this infection and pathogenic *BRCA* mutations.

Testing for *BRCA1* and *BRCA2* mutations can include targeted analysis for pathogenic founder variants in at-risk populations (e.g., individuals with Ashkenazi Jewish ancestry), sequence analysis and duplication/deletion analysis of *BRCA1* and *BRCA2*, or a multigene panel. *BRCA1* accounts for approximately 66% of *BRCA1/BRCA2*-associated hereditary breast and ovarian cancer syndrome (HBOC) cases. Sequence analysis can identify variants in approximately 87% to 89% of cases for *BRCA1* and 97% to 98% of cases for *BRCA2*. Gene-targeted duplication/deletion testing identifies variants in 11% to 13% of cases for *BRCA1* and 2% to 3% for *BRCA2* (Petrucelli et al., 2025). The risk of developing breast and ovarian cancer is significantly increased in individuals who inherit a harmful variation in *BRCA1* or *BRCA2*; over 60% of women with these variants will develop breast cancer in their lifetime compared with only 13% of women in the general population. Women with *BRCA1* and *BRCA2* variations are also at increased risk of developing

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cancer in the contralateral breast in the future. Overall, 39% to 58% of women with a harmful mutation in *BRCA1* and 13% to 29% of women with a harmful mutation in *BRCA2* will develop ovarian cancer (including fallopian tube cancer and primary peritoneal cancer) in their lifetime compared with only 1.1% of women in the general population. There is also evidence that variations in *BRCA1* and *BRCA2* genes are related to increased risk of pancreatic cancer, prostate cancer, and other cancers such as melanoma, gastric cancer, and uterine serious carcinoma (National Cancer Institute, 2024).

Several studies have shown that *BRCA1* breast cancer is more likely to be characterized as triple negative. Studies have reported *BRCA1* pathogenic/likely pathogenic (P/LP) variants in 4.4% to 16% of individuals with triple-negative breast cancer. In addition, it appears that among individuals with triple-negative disease, *BRCA* mutation carriers are diagnosed at a younger age than noncarriers (NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate v1.2026). A study of 54 women aged 40 years or younger with triple-negative breast cancer who were not considered candidates for *BRCA* testing because of the lack of a strong family history revealed that five of the women had *BRCA1* mutations, and one of the women had a *BRCA2* mutation (11% mutation prevalence) (Young et al., 2009). In a cohort of individuals with triple-negative breast cancer (median age, 51 years), Gonzalez-Angulo et al. (2011) found a 19.5% incidence of *BRCA* mutations. The authors recommended that genetic testing be discussed with all individuals diagnosed with triple-negative breast cancer.

To investigate the significance of *BRCA1/2* mutations in familial pancreatic cancer (FPC), Limijadi et al. (2024) performed a systematic review and meta-analysis of nine diagnostic studies, including 4,267 individuals from the US, Italy, and Poland. The length of the research period for the studies varied from a minimum of 2 years to a maximum of 36 years, with an average duration of 14 years. Based on their analysis, the reviewers asserted that *BRCA1/2* testing benefits first-degree relatives of individuals with FPC, who have 2 to 10 times higher risk of developing FPC than the general population. Identifying *BRCA1/2* mutations is important not only for FPC risk but also for broader cancer risks such as HBOC. *BRCA1/2* testing has also been shown to be beneficial in individuals with FPC for whom poly-ADP ribose polymerase (PARP) inhibitors could lead to better clinical outcomes, as previous studies have demonstrated that the presence of *BRCA1/2* mutations in pancreatic cancer strongly correlates with improved overall survival compared with mutation-free pancreatic cancer due to targeted treatment options (Toss et al., 2019; Puccini et al., 2022). The authors recommended *BRCA1/2* testing for diagnostic and prognostic purposes for first-degree relatives of individuals who are diagnosed with FPC and encouraged further study, with large sample sizes and long-term follow-up, to validate their findings and to better understand the drivers for differential treatment responses between individuals with FPC who have *BRCA1/2* mutations and those without these mutations.

The prevalence of *BRCA1/2* large rearrangements (LRs) was investigated in 48,456 individuals with diverse clinical histories and ancestries who were referred for molecular testing due to suspicion of HBOC. Prevalence data were analyzed for individuals from different risk and ethnic groups. Individuals were designated as high risk (n = 25,535) if their clinical history predicted a high prior probability. For these individuals, LR testing was performed automatically in conjunction with sequencing. Individuals who did not meet the high-risk criteria (elective, n = 22,921) underwent LR testing if *BRCA1/2* sequencing indicated no known mutations. Overall, *BRCA1/2* mutation prevalence among individuals considered high risk was 23.8% vs 8.2% in the elective group. The mutation profile in individuals at high risk was 90.1% sequencing mutations vs 9.9% LRs and for elective individuals was 94.1% sequencing vs 5.9% LRs. The authors noted that this difference may reflect the bias in individuals at high risk to carry mutations in *BRCA1*, which has a higher penetrance and frequency of LRs than *BRCA2*. Significant differences in the prevalence and types of LRs were found in individuals of different ancestries, with LR mutations significantly more common in individuals of Latin American/Caribbean descent (Judkins et al., 2012).

Of 211 Ashkenazi Jewish probands with breast cancer and a family history of pancreatic cancer, Stadler et al. (2012) found that 30 (14.2%) harbored a *BRCA* mutation. Fourteen of the mutations (47%) were in *BRCA1*, and 16 (53%) were in *BRCA2*. Individuals diagnosed with breast cancer at 50 years of age or younger were found to have a higher *BRCA1/2* mutation prevalence than those with breast cancer who were diagnosed at greater than 50 years of age (21.1% vs 6.9%). In individuals with a first-, second-, or third-degree relative with pancreatic cancer, the mutation prevalence was 15.4%, 15.3%, and 8.6%, respectively. The authors found that *BRCA1* and *BRCA2* mutations were observed with nearly equal distribution in Ashkenazi Jewish families with breast and/or pancreas cancers, suggesting that both genes are associated with pancreatic cancer risk.

Ferrone et al. (2009) looked at the prevalence of *BRCA1* and *BRCA2* in an unselected group of individuals of Jewish descent and compared individuals with resected *BRCA* mutation–associated pancreatic adenocarcinoma (PAC) with those with PAC but no identified mutations. Of the 187 individuals of Jewish ancestry who underwent resection for PAC, tissue was available for 145. Founder mutations for *BRCA1* and *BRCA2* were identified in 5.5% of individuals [two with *BRCA1* (1.3%) and six with *BRCA2* (4.1%)]. A previous cancer was reported by 24% of individuals (35/145), with the most

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common sites being breast [9/35 (74%)] and prostate [8/35 (23%)]. These findings led the researchers to conclude that *BRCA2* mutations are associated with a higher risk of PAC.

Hereditary Breast, Ovarian, Pancreatic, and Prostate Cancer Multigene Panels

A 2024 weighted meta-analysis by Rowlands et al. synthesized germline genetic data from three large, population-based case-controlled studies: BRIDGES, CARRIERS, and UK Biobank. The analysis included data from 101,397 women with breast cancer and 312,944 controls. The goal was to assess the frequency and risk association of 37 potential breast cancer susceptibility genes in women with population-type breast cancer, meaning cases were not selected based on family history, early onset, or other risk factors. Strong associations were found in genes considered high risk (*BRCA1*, *BRCA2*, and *PALB2*), while moderate-risk genes *CHEK2* and *ATM* had lower odds ratios but stronger associations with estrogen receptor (ER) positive breast cancer. Low-frequency genes (*RAD51C*, *RAD51D*, and *BARD1*) had modest associations but were more strongly linked to triple-negative breast cancer. Syndromic genes *TP53*, *STK11*, *CDH1*, *PTEN*, and *NF1* had very low frequencies in population-based studies and only modest associations, which suggested limited usefulness for broad panel testing in unselected populations. The remaining genes showed no statistically significant associations with population-type breast cancer in this investigation. Many current breast cancer panels comprise large numbers of genes, some of which have very low pathogenic variant (PV) frequency and only modest associations, which reduces their overall utility; the authors asserted that the outcomes of this study will be helpful to define which genes should be included in panels for use in population-based testing. Despite its strengths, which included large, diverse cohorts, a population-based design, and gene-level risk estimates (including carrier frequencies and odds ratios for 37 genes), this analysis had several limitations. These include (1) potential population bias, with most data coming from White/European populations; (2) missing data such as receptor status (e.g., ER-positive, triple negative); (3) the limitation of the study to 37 preselected genes, which could exclude emerging genes or genes that are less studied; and (4) variations in sequencing methodologies across studies included in the analysis, which could introduce variability in the results. Ongoing efforts are required to determine the optimal selection of genes for inclusion in germline testing for population-based evaluation to ensure overall clinical benefit.

In a recent cohort study, Whitworth et al. (2022) sought to answer the following question: “Could all individuals with breast cancer benefit from multigene germline genetic testing?”. Currently, NCCN guidelines recommend germline testing for high-risk genes in individuals diagnosed with breast cancer when certain criteria are met. This study evaluates the potential effect of universal testing in participants with breast cancer on clinical decision-making. The study included 952 participants between the ages of 18 and 90 years who had a diagnosis of breast cancer and had not previously undergone either single-gene or multigene testing. Participants were evaluated as in criteria or out of criteria, as per the 2017 NCCN guidelines; testing was then performed using a multigene germline test panel (80 genes). Clinicians from a combination of 20 community and academic locations assessed and recorded clinical information and changes to clinical recommendations based on test results. Relationships between previously unreported clinical features (including BRCAPRO scores) and P/LP prevalence were ascertained. Clinician-reported recommendations for 939 (467 in criteria and 472 out of criteria) of the participants with breast cancer were made available. Among participants found to have a P/LP variant, changes in recommended management were reported for 83.8% (31/37) of in-criteria participants and 67.6% (23/34) of out-of-criteria participants. Testing results led to a change in recommendations for 63.6% (14/22) of out-of-criteria participants with a variant in a breast cancer predisposition gene. Multigene testing was considered helpful for two-thirds of participants with P/LP variants and for one-third of the participants with results that were either negative or found variants of uncertain significance (VUSs). No changes were made for 98.9% of participants with negative results or VUSs. The researchers concluded that universal germline testing provides useful information for clinical decision-making and leads to targeted treatments and/or clinical trials for all individuals diagnosed with breast cancer. However, limitations were noted, including the lack of documentation of cancer stage at diagnosis; additionally, study sites were primarily breast surgery practices, so participants who were included in the study were biased toward early-stage, resectable disease. In addition, the study was performed prior to the NCCN guideline update, allowing screening of participants for PARP inhibitor treatment eligibility. The out-of-criteria population is skewed to participants older than 45 years (per NCCN guideline requirements), and no ongoing follow-up for determination of longer-term outcomes was included. Lastly, the study was sponsored by a multigene test manufacturer, and several of the authors had affiliations with the sponsor, creating a potential for bias.

Hayes (2021; updated 2024) reported on the evidence for use of genetic testing to detect both high and moderate hereditary cancer risk gene variants in women with new diagnoses of breast cancer, regardless of other risk factors. An overall low to moderate quality of evidence (including five studies) found that use of gene testing for high-risk breast cancer genes identified a small number of women who would not have been recognized with standard clinical criteria for selection of candidates for testing. Hayes suggested that there is probable clinical utility for high-risk gene screening in women with breast cancer who are not preselected for other risk factors. In the case of testing for moderate gene variants, evidence for clinical utility is uncertain.

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Alvarado et al. (2020) evaluated 3,162 women for the prevalence of P/LP, with the same multigene cancer panel, including 20 genes. The majority of women (65.4%) were post breast or ovarian cancer diagnosis. The overall prevalence of any P/LP result was 11.7%, with nearly 5.4% having *BRCA1/2* mutations, while 6.3% had at least one mutation in non-*BRCA* genes. In those with only a P/LP result, 55% of the total mutations were non-*BRCA*. The researchers concluded that multigene cancer panel testing may be appropriate in a high-risk cohort.

Corredor et al. (2020) evaluated women with multiple primary breast cancers using panel testing to determine the rate of non-*BRCA* mutations. Overall, 85 women were tested with a multigene panel, and of them, 33 (38.8%) tested positive for a pathogenic mutation, including nine women with *BRCA1* mutations, five with *BRCA2* mutations, five with *ATM* mutations, one with a *BARD1* mutation, four with *CHEK2* mutations, one with an *MSH2* mutation, one with an *MSH6* mutation, two with *PALB2* mutations, one with a *PMS2* mutation, one with a *PTEN* mutation, and three with *TP53* mutations. Overall, 17.6% tested positive for a non-*BRCA* breast cancer predisposition gene.

Lee et al. (2019) reviewed several genes on HBOC susceptibility test panels that have not been fully evaluated for strength of association with disease. The researchers used the Clinical Genome Resource Clinical Validity framework to calculate the strength of evidence between selected genes and breast or ovarian cancer. A total of 31 genes were selected for evaluation of the relationship between the gene and breast cancer, and 32 genes were selected for ovarian cancer. The relationship was then classified as definitive, strong, moderate, limited, refuted, disputed, or no reported evidence. Of the genes, definitive clinical validity classifications were made for 10 of 31 and 10 of 32 gene-disease pairs for breast and ovarian cancer, respectively. Only two genes had a moderate classification. In the limited group, six of 31 for breast cancer and six of 32 for ovarian cancer were defined. Inconsistent evidence resulted in disputed or refuted assertions for nine of 31 genes for breast and four of 32 genes for ovarian cancer. No reported evidence of disease association was found for five of 31 genes for breast and 11 of 32 for ovarian cancer.

Shimelis et al. (2018) aimed to define the cancer genes associated with an increased risk of triple-negative breast cancer. A large cohort of participants with triple-negative breast cancer was assembled, and multigene panel testing (MGPT) of 21 genes in 8,753 participants was performed by a clinical testing laboratory (Ambry Genetics, Aliso Viejo, CA). Additionally, testing of 17 genes in 2,148 participants from a previous Triple-Negative Breast Cancer Consortium study was included. The study found that germline PVs in *BARD1, BRCA1, BRCA2, PALB2,* and *RAD51D* were associated with a high risk (odds ratio, > 5.0) of TNBC and a greater than 20% lifetime risk of overall breast cancer among Caucasian participants. PVs in *BRIP1, RAD51C*, and *TP53* were associated with a moderate risk (odds ratio, > 2) of triple-negative breast cancer. Comparable trends were observed in the African American population. PVs in these triple-negative breast cancer genes were detected in 12.0% (3.7% non-*BRCA1/2*) of all participants. The researchers concluded that multigene hereditary cancer panel testing can identify genes associated with an elevated risk of triple-negative breast cancer.

Crawford et al. (2017) evaluated 300 women who had previously tested negative for PVs in *BRCA1/2* by either limited or comprehensive sequencing. All the study participants met additional criteria, including (1) a personal history of bilateral breast cancer, (2) a personal history of breast cancer and a first- or second-degree relative with ovarian cancer, or (3) a personal history of ovarian, fallopian tube, or peritoneal carcinoma. The testing determined that 9% of the total population of the study had pathogenic mutations associated with heritable cancer risk, and 8% had mutations in genes other than *BRCA1/BRCA2*. Elevated pathogenic mutation rates in genes other than *BRCA1/2* were found in women of Ashkenazi Jewish and Hispanic descent (12% and 18%, respectively). The researchers concluded that individuals who have tested negative for *BRCA1/2* mutations but meet the additional criteria (outlined above) should be candidates for subsequent MGPT, which has important implications for family testing.

Clinical Practice Guidelines

American College of Medical Genetics and Genomics (ACMG)

In a 2020 statement, the ACMG explored the evidence supporting *BRCA1/2* and other inherited breast cancer genetic testing for all patients diagnosed with breast cancer (Pal et al., 2020). Although they recommended that all patients with breast cancer be evaluated for the need for germline genetic testing for hereditary breast cancer, the ACMG statement indicates that the current evidence does not support the use of genetic testing for every patient diagnosed with breast cancer, especially in the case of multigene panels that include genes lacking evidence to support a change in medical management. When performed, genetic testing for inherited breast cancer should include full gene sequencing, deletion/duplication analysis, and detection of known P/LP variants in an appropriately accredited genetic testing laboratory. When a P/LP variant is found in moderately penetrant breast cancer genes, guidance will be based on consensus recommendations. Enhanced screening has not yet been associated with enhanced survival or earlier identification of disease. The implications of genetic testing should be carefully discussed with patients during genetic counseling with a trained genetics professional or a health care provider with expertise in cancer genetics, and any patient

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found to have a P/LP variant in established breast cancer genes should be educated about the importance of cascade testing of family members.

American College of Obstetricians and Gynecologists (ACOG)

In 2019 (reaffirmed 2020), ACOG published Committee Opinion 793 titled Hereditary Cancer Syndromes and Risk Assessment. The document included recommendations for genetic testing, including:

- A hereditary cancer risk assessment is the key to identifying patients and families who may be at increased risk of developing certain types of cancer. Assessments should be performed by obstetrician-gynecologists or other obstetric-gynecologic care providers and should be updated regularly.
- If a hereditary cancer risk assessment suggests an increased risk of a hereditary cancer syndrome, referral to a specialist in cancer genetics or a health care provider with expertise in genetics is recommended for expanded gathering of family history information, risk assessment, education, and counseling, which may lead to genetic testing and tailored cancer screening, risk reduction measures, or both.
- Genetic testing may be performed using a panel of multiple genes through next-generation sequencing (NGS) technology. This multigene testing process allows for testing for P/LP variants in multiple genes that may be associated with a specific cancer syndrome or family cancer phenotype (or multiple phenotypes). It also increases the likelihood of finding VUSs.

In practice bulletin 182 (2017; reaffirmed 2019), ACOG provided guidance for genetic evaluation of HBOC syndrome. Their recommendations address women with the following:

- A close relative (mother, sister, daughter, grandmother, granddaughter, aunt, or niece) with a known *BRCA* mutation, a first-degree relative or several close relatives who meet one or more of the criteria below, or a close relative with male breast cancer.
- A personal history of the following:
  - Ovarian cancer.
  - Breast cancer at age 45 years or less.
  - Breast cancer and a close relative with breast cancer at age 50 years or less or a close relative with ovarian cancer at any age.
  - Breast cancer at age 50 years or less, with a limited or unknown family history.
  - Breast cancer and two or more close relatives with breast cancer at any age, pancreatic cancer, or prostate cancer.
  - Two breast cancer primaries, with the first diagnosed before age 50 years.
  - Triple-negative breast cancer at age 60 years or less.
  - Breast cancer and Ashkenazi Jewish ancestry.
  - Pancreatic cancer and two or more close relatives with a BRCA-related cancer.

Additionally, in the 2017 Committee Opinion 716 (reaffirmed 2021), ACOG recommends that women with a strong family history of ovarian, breast, or colon cancer may have a *BRCA* mutation or Lynch syndrome (LS) and should be referred for formal genetic counseling to assess their cancer risk, and if appropriate, be offered testing.

American Society of Breast Surgeons (ASBrS)

An ASBrS consensus statement (2019) made several recommendations regarding the genetic assessment of hereditary risk for breast cancer, including:

- Breast surgeons, genetic counselors, and other medical professionals knowledgeable in genetics can provide patient education and counseling, although when the patient's history and/or test results are complex, referral to a certified genetic counselor or genetics professional may be helpful.
- Multigene panels are increasingly available for screening purposes. Consensus among experts regarding which genes should be tested in different clinical scenarios is lacking.
- Genetic testing should be made available to all patients with a personal history of breast cancer.
- Patients who have had genetic testing previously may benefit from updated testing.
- Genetic testing should be made available to patients without a history of breast cancer when the NCCN guidelines are met. Unaffected patients should be informed that testing an affected relative first, whenever possible, is more informative than undergoing testing themselves.
- VUSs are not clinically actionable and are considered inconclusive. Patients should be managed on their risk factors and not a VUS result.

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American Society of Clinical Oncology (ASCO)

In a 2025 ASCO guideline, Yu et al. recommend both germline and somatic DNA sequencing for patients with metastatic prostate cancer using panel-based assays, noting that germline testing results may have implications such as identifying the need for additional cancer screening as well as the need for cascade testing for family members (evidence quality: high; strength of recommendation: strong).

ASCO published a guideline for genetic testing in women with a diagnosis of epithelial ovarian cancer (Konstantinopoulos et al., 2020). This was the result of a systematic review of 19 identified studies, including randomized controlled trials, comparative observational studies, systematic reviews, and meta-analyses published from 2007 through 2019. Per the ASCO guideline, all women with epithelial ovarian cancer should undergo germline genetic testing for *BRCA1/2* and other ovarian cancer susceptible genes (e.g., multigene panel that includes, at a minimum, *BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, MLH1, MSH2, MSH6, PMS2*, and *PALB2*). In women without *BRCA1/2* variants, somatic tumor testing for *BRCA1/2* variants should be performed. Health care providers familiar with the diagnosis and management of hereditary cancer should conduct the genetic evaluations, and first- or second-degree blood relatives of a patient with ovarian cancer and a known gene variant should be offered counseling, evaluation, and testing as well. VUSs should not drive clinical decision-making.

ASCO convened an expert panel to determine recommendations for male breast cancer management and published the results (Hassett et al., 2020). The panel used 26 studies as the basis of the recommendations. While the majority of the recommendations concerned treatment options, the panel recommended that “genetic counseling and germline genetic testing of cancer predisposition genes should be offered to all men with breast cancer” (evidence quality: low; strength of recommendation: strong).

American Society of Clinical Oncology (ASCO)/Society of Surgical Oncology (SSO)

In 2024, ASCO and the SSO (Bedrosian et al.) published recommendations for germline mutation testing for patients diagnosed with breast cancer. These recommendations were developed through a systematic review and formal consensus process undertaken by a designated multidisciplinary panel of joint ASCO and SSO experts. A total of 47 articles met eligibility requirements for inclusion in the analysis for germline mutation recommendations, and 18 articles were evaluated for genetic counseling recommendations. As a result of the review and discussion, the following recommendations for germline genetic testing were made:

- Patients 65 years of age or younger and newly diagnosed with breast cancer (stage I-III or de novo stage IV/metastatic disease) should be offered BRCA1/2 testing (formal consensus; agreement: 87.50%).
- Patients older than 65 years of age diagnosed with breast cancer (stage I-III or de novo stage IV/metastatic disease) should be offered BRCA1/2 testing if they:
  - Are candidates for PARP inhibitor therapy for early-stage or metastatic disease.
  - Have triple-negative breast cancer.
  - Have a personal or family history suggesting the possibility of a PV.
  - Were assigned male sex at birth.
  - Are of Ashkenazi Jewish ancestry or are members of a population with an increased prevalence of founder mutations (formal consensus; agreement: 92.50%).
- Patients undergoing *BRCA1/2* testing should be offered testing for other hereditary cancer predisposition genes to be determined by their individual or family history (formal consensus; agreement: 90%).
- Any patient with recurrent breast cancer (local or metastatic) who is a candidate for PARP inhibitor therapy should be offered *BRCA1/2* testing, regardless of their family history (formal consensus; agreement: 97.50%).
- Patients with a second primary cancer, either in the contralateral or ipsilateral breast, should be offered *BRCA1/2* testing (formal consensus; agreement: 89.74%).
- Patients with a personal history of breast cancer diagnosed at 65 years of age or younger who currently do not have active disease should be offered *BRCA1/2* testing if the result will inform their personal risk management or a family risk assessment (formal consensus; agreement: 90%).
- Patients with a personal history of breast cancer diagnosed at age 66 years or older who currently do not have active disease but meet one of the following criteria should be offered *BRCA1/2* testing if the result will inform their personal risk management or a family risk assessment:
  - Their personal or family history suggests the possibility of a PV.
  - They were assigned male sex at birth.
  - They had triple-negative breast cancer.
  - They are of Ashkenazi Jewish ancestry or are members of a population with an increased prevalence of founder mutations (type: formal consensus; agreement: 94.87%).
- Undergoing testing for high-penetrance genes beyond BRCA1/2 (including PALB2, TP53, PTEN, STK11, and CDH1) may be helpful for clinical decision-making and could help refine estimates of the risk of second primary cancer as

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well as inform family risk assessment. Therefore, this testing should be offered to appropriate candidates (formal consensus; agreement: 92.31%).
- Although there is no benefit for treatment of the index breast cancer from testing moderate-penetrance breast cancer genes, the risk of second primary cancer or family risk assessment may be informed by such testing and may be offered to patients undergoing BRCA1/2 testing, when appropriate (formal consensus; agreement: 87.50%).
- A patient's personal and family history should be considered if a multigene panel is ordered (formal consensus; agreement: 91.43%).
- VUSs should not change management (formal consensus; agreement: 88.57%).

The importance of individualized genetic consultation and counseling for selection of the appropriate test and assistance with interpretation and communication of results to the affected patient and/or family is highlighted.

European Society for Medical Oncology (ESMO)

ESMO's recent clinical practice guidelines for the diagnosis, treatment, and follow-up of early breast cancer (Loibl et al., 2024) recommend germline testing and genetic counseling for patients with PVs in *BRCA1/2* who meet national criteria guidelines and/or those who are candidates for olaparib therapy.

A 2023 ESMO clinical practice guideline (Sessa et al.) addresses risk reduction and screening for cancer in HBOC syndrome. Per this guideline, germline genetic testing with multigene panels should be offered to patients with significant family history (grade of recommendation: A). Panels should comprise clinically validated HBOC genes (*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, PALB2, PTEN, RAD51C, RAD51D, STK11, and TP53*). The authors highlight that screening panels that are marketed today incorporate genes beyond *BRCA1/2*, and associated cancer risk varies greatly with each gene. The importance of comprehensive genetic counseling to differentiate risks associated with various HBOC-associated genes is highlighted.

National Comprehensive Cancer Network (NCCN)

The NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate Cancer guidelines (v1.2026) present evidence-based criteria for genetic testing for hereditary breast, ovarian, and/or pancreatic cancer, noting that a patient's personal and/or family history can often be explained by more than just one inherited cancer syndrome. Multigene testing simultaneously evaluates genes for hereditary cancer types associated with a specific family phenotype (or multiple phenotypes). Phenotype-directed testing using tailored, multigene panel tests can be more efficient and cost effective and increase potential for detection of P/LP variants in patients at risk. For patients who have tested negative for a single syndrome but whose personal/family history suggests hereditary susceptibility, such testing may also prove to be helpful. These guidelines address genetic risk assessment, counseling, testing, and management based on test results. Testing recommendations are separated into three categories: (1) clinically indicated; (2) may be considered; and (3) low probability that testing will find documented high-penetrance genes.

Per the NCCN guidelines, hereditary cancer testing is clinically indicated for the following general situations:
- A patient has any blood relative with a known P/LP variant in a cancer susceptibility gene
- A patient has previously tested negative with limited testing (e.g., single-gene or absent deletion duplication analysis), meets testing criteria below, and desires multigene testing
- A known P/LP variant has been identified on tumor genomic testing that has clinical implications if also identified in the germline
- Testing is performed to aid in systemic therapy and surgical decision-making
- A patient meets Li-Fraumeni syndrome, Cowden syndrome/PTEN hamartoma tumor syndrome, or LS testing criteria

Testing may be considered in patients of Ashkenazi Jewish ancestry without other risk factors or in those with a personal history of serous endometrial cancer (EC).

Breast Cancer

For patients with a personal or family history of breast cancer, testing for high-penetrance breast cancer susceptibility genes (e.g., *BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11*, *TP53*) is clinically indicated in the following situations (also see general testing criteria above):
- Patient has a personal history of breast cancer with the following features:
  - Diagnosed at ≤ 50 years old.
  - Diagnosed at any age and:
    - Used for treatment indications.
      - Testing will aid in treatment decisions involving PARP inhibitors in the metastatic setting; or

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        - Testing will aid in adjuvant treatment decisions with olaparib for high-risk, HER2-negative breast cancer.
    - Pathology/histology includes:
        - Triple-negative breast cancer.
        - Multiple primary breast cancer (synchronous or metachronous).
        - Lobular breast cancer with personal or family history of diffuse gastric cancer.
    - Breast cancer in a patient assigned male at birth.
    - Patient is of Ashkenazi Jewish ancestry.
    - Patient has at least one close blood relative and:
        - Relative diagnosed with breast cancer at age 50 years or younger.
        - Relative has breast cancer and was assigned male at birth.
        - Relative was diagnosed with ovarian, pancreatic, or metastatic or high- or very-high risk group prostate cancer.
    - Presence of at least three total diagnoses (including patient with breast cancer) of breast and/or prostate cancer (any grade) on the same side of the family.
- Patient is unaffected or affected but does not meet the criteria above and:
    - Has a first- or second-degree blood relative who meets any of the above criteria (except unaffected patients whose relatives meet criteria only for systemic therapy decision-making).
    - Has a probability of > 5% of a *BRCA1/2* P/LP variant based on prior probability models (e.g., Tyrer-Cuzick, BRCAPRO, CanRisk).

Testing may be considered with appropriate counseling and management in the following situations:
- Patient has a personal history of breast cancer at age 65 years or younger and does not meet any of the above criteria. *Caution: The majority of those PVs will be in moderate-penetrance genes, which are overrepresented in older affected patients. Access to an experienced genetic counseling team to discuss management options is especially important in this setting.
- Patient has a personal history of breast cancer diagnosed at any age, with one or more close blood relatives with intermediate-risk prostate cancer with intraductal/cribriform histology.
- Patient is unaffected or affected but does not meet any of the above criteria and has a 2.5% to 5% probability of a BRCA1/2 P/LP variant, based on prior probability models (e.g., Tyrer-Cuzick, BRCAPRO, CanRisk).
- Patient has a personal history of malignant phyllodes tumors.

There is a low probability (less than 2.5%) that testing will identify high-penetrance genes in the following situations:
- Patient assigned female at birth who has been diagnosed with breast cancer at greater than 65 years of age, with no close relatives with breast, ovarian, pancreatic, or prostate cancer.
- Patient is diagnosed with localized prostate cancer, with a Gleason score of < 7, and has no close relatives with breast, ovarian, pancreatic, or prostate cancer.

Note: Consideration of the limitations of unknown or limited family structure is indicated in those aged ≥ 51 years.

Ovarian Cancer

For patients with a personal or family history of ovarian cancer, testing for ovarian cancer susceptibility genes [e.g., *ATM, BRCA1, BRCA2, BRIP1*, LS genes (*MLH1, MSH2, MSH6, EPCAM)*, *PALB2, RAD51C*, *RAD51D*] is clinically indicated in the following situations (also see general testing criteria above):
- Patient has a personal history of epithelial ovarian cancer (including fallopian tube or peritoneal cancer) diagnosed at any age.
- Patient has a personal history of nonepithelial ovarian cancer [sex-cord tumor with annular tubules, small cell carcinoma of the ovary (hypercalcemic type)] at any age.
- Patient is unaffected with ovarian cancer and has a family history, including one of the following:
    - Patient has a first- or second-degree blood relative with epithelial ovarian cancer (including fallopian tube or peritoneal cancer) diagnosed at any age.
    - Patient does not meet the criteria above but has a probability of > 5% of a *BRCA1/2* P/LP variant, based on prior probability models (e.g., Tyrer-Cuzick, BRCAPRO, CanRisk).

Testing may be considered with appropriate counseling and when a patient has a personal history of serous tubal intraepithelial carcinoma diagnosed at any age.

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Pancreatic Cancer

For patients with a personal or family history of pancreatic cancer, testing for pancreatic cancer susceptibility genes [e.g., *ATM, BRCA1, BRCA2, CDKN2A*, LS genes (*MLH1, MSH2, MSH6, EPCAM*), *PALB2, STK11*, *TP53*] is clinically indicated in the following situations (also see general testing criteria above):

- Patient has a personal history of exocrine pancreatic cancer (including acinar cell carcinoma) or neuroendocrine pancreatic cancer.
- Patient has a first-degree relative diagnosed with exocrine pancreatic cancer.
- Patient has a neuroendocrine pancreatic tumor.

Prostate Cancer

For patients with a personal or family history of prostate cancer, testing for prostate cancer susceptibility genes (e.g., *ATM, BRCA1, BRCA2, CHEK2, HOXB13*, *PALB2*, *TP53)* is clinically indicated in the following situations (also see general testing criteria above):

- Patient has a personal history of prostate cancer with the following features:
  - Tumor is:
    - Metastatic.
    - In the high- or very-high risk group.
  - Patient has ancestry/family history, including:
    - At least one close blood relative with:
      - Breast cancer diagnosed age 50 years or younger.
      - Breast cancer in a patient assigned male at birth at any age.
      - Ovarian cancer at any age.
      - Pancreatic cancer at any age.
      - Metastatic, node-positive, or high- or very-high risk group prostate cancer at any age.
    - At least three close blood relatives with breast cancer and/or prostate cancer (any grade) on the same side of the family (including the patient with prostate cancer).
    - Ashkenazi Jewish ancestry.
- Patient is unaffected or affected but does not meet the above criteria and has a first-degree blood relative who meets any of the criteria above (except unaffected patients whose relatives meet criteria only for systemic therapy decision-making).

Testing for prostate cancer susceptibility genes may be considered when a patient has a personal history of prostate cancer; and:

- Patient was diagnosed at age 55 years or younger but does not meet the above criteria.
- Patient was diagnosed with intermediate-risk prostate cancer with intraductal/cribriform histology at any age.

National Society of Genetic Counselors (NSGC)

In their 2023 position statement, the NSGC endorses the use of multigene panels when such testing is “clinically warranted and appropriately applied.” Providers are encouraged to thoroughly assess the analytical and clinical validity of the test as well as its clinical utility.

In 2021, the NSGC published a new practice resource that notes the growing body of research that has emerged related to expanded genetic testing of genes other than *BRCA1* and *BRCA2* and the impact on risk assessment, psychosocial issues, medical management, and genetic assessment in patients from families with moderate- or high-risk breast and/or ovarian cancer (Berliner et al., 2021). The practice resource indicates that little is known about clinical management for patients with P/LP variants in less common, high-penetrance or moderate-penetrance genes, and research is ongoing in this area.

The NSGC recommends the following steps for cancer risk assessment:

- Gathering personal medical and family history data
- Psychosocial assessment
- Providing education focused on the basic principles of genetics and cancer
- Discussion of cancer and P/LP risk and how personalized risk estimates are derived
- Facilitation of the informed consent process through discussion of the risks, benefits, limitations, and likelihood of identifying a mutation with genetic susceptibility testing
- Results disclosure (if applicable)
- Discussion of medical management options

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- Discussion of dissemination of information regarding testing performed and implications on testing of other family members
- Review of issues related to genetic discrimination

U.S. Preventive Services Task Force (USPSTF)

In 2019, the USPSTF updated the recommendations for risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancers. The updated document recommends that primary care providers screen women who have a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with *BRCA1/2* mutations. This screening should be performed with one of several screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful mutations in breast cancer susceptibility genes (*BRCA1* or *BRCA2*). Tools evaluated by the USPSTF include the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, 7-Question Family History Screening Tool, International Breast Cancer Intervention Study instrument (Tyrer-Cuzick), and brief versions of the BRCAPRO. Women with positive screening results should receive genetic counseling and, if indicated after counseling, genetic testing (grade B recommendation).

In addition, the USPSTF (2019) recommends against routine genetic counseling or *BRCA* testing for women in whom a personal or family history or ancestry is not associated with an increased risk for potentially harmful mutations in the *BRCA1* or *BRCA2* genes (grade D recommendation).

High-Risk Colorectal, Endometrial, and Gastric Cancer Syndromes (Including Lynch Syndrome-Associated Cancers)

To determine the yield and possible impact of MGPT on clinical decision-making, Coughlin et al. (2022) conducted a retrospective cohort study, including 34,244 patients with a history of colorectal cancer (CRC). All patients underwent MGPT using panel tests containing at least 10 genes. The patients were largely female (60.7%), White (70.6%), and 50 years of age or older (68.9%). A total of 4,864 patients (14.2%) were found to have one or more P/LP germline variants, and 3,111 (9.1%) had a variant that is associated with increased CRC/polyposis risk. Another 3.1% had an otherwise clinically actionable P/LP variant. Notably, there was not a clear association between larger gene panels and a higher yield of clinically actionable P/LP variants. P/LP variants were more common in those with Hispanic ethnicity ($p < 0.001$) and in patients of Ashkenazi Jewish descent ($p < 0.001$). The overall rate of clinically actionable P/LP variants found on MGPT across all panel sizes, races, and ages was at least 7.9%. VUSs were identified in 13,094 patients (38.2%). Based on these results, the authors concluded that MGPT in patients with CRC identified high rates of clinically actionable variants across all ages and racial/ethnic groups, regardless of panel size, which supports expanding germline genetic testing guidelines for these individuals. Noted limitations include the collection of data from test requisition forms, limiting confirmation of clinical information, and the inclusion of all patients with CRC, even if CRC was not the primary reason for the patient to undergo genetic evaluation.

In a 2021 publication, Uson et al. (included in the 2023 Hayes Precision Medicine Insight Report discussed below) reported that using universal MGPT instead of practice guideline criteria–based testing in CRC was associated with a small but significant increase in finding heritable gene mutations. To conduct this study, the authors used a prospective, multisite design and a > 80-gene NGS platform to perform testing in participants with CRC. A total of 361 adults participated (median age, 57 years). Pathogenetic germline variants were found in 15.5% (n = 56) of participants in the study, and 9.4% (n = 34) had clinically actionable findings that would not have been detected with a CRC-specific gene panel or if standard clinical practice criteria had been followed. Overall, 11% (one in 10) had changes in their management based on test results. Family cascade testing was low (16%), which is a concerning observation and will require further study. Another concern is the demographic of the participants seen at the Mayo Clinic sites at which the study was conducted, which may limit the generalization of study results. Family history was self-reported, which may also limit accuracy and completeness, and the follow-up was relatively short, impacting the utility of survival analysis to address outcomes fully. Lastly, the study was not able to track blood relatives who may have undergone cascade testing elsewhere. The researchers caution that further long-term follow-up will be necessary to address outcomes on morbidity and cancer care decision-making.

Gupta et al. (2019) published insights regarding the NCCN updated guidelines for susceptibility screening for CRC syndromes, specifically around multigene cancer panels for hereditary CRC syndromes. For polyposis syndromes that include familial adenomatous polyposis, attenuated familial adenomatous polyposis, *MUTYH*-associated polyposis, and other rare genetic causes of multiple adenomatous polyps, data suggested that there are many genes that may contribute to CRC risk, including *AXIN2, GREM1, NTHL1, POLE, POLD1*, and *MSH3*. Likewise, many genes have been linked to LS, which is associated with an increased risk for colon, endometrial and ovarian, gastric, pancreatic, biliary tract, ureter, renal pelvis, small intestine, and brain cancers (usually glioblastoma) as well as sebaceous adenomas, sebaceous

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carcinomas, and keratoacanthomas, as seen in the Muir-Torre syndrome variant. The use of a multigene panel can help with the identification of LS and manage the future risk of CRC and EC. The panel recommends universal screening in all individuals with CRC or EC at any age with a tumor showing evidence of mismatch repair deficiency (dMMR), either by microsatellite instability or loss of mismatch repair (MMR) protein expression.

Using the Clinical Genome Resource Clinical Validity framework, Seifert et al. (2019) evaluated gene-disease associations in hereditary CRC. This study assessed 42 gene-disease pairs. Of all gene-disease pairs evaluated, 14 of 42 (33.3%) were definitive, one of 42 (2.4%) was strong, six of 42 (14.3%) were moderate, 18 of 42 (42.9%) were limited, and three of 42 (7.1%) were either no reported evidence, disputed, or refuted. The researchers stated that providers should recognize that less than 60% of genes on available panels have strong or definitive evidence of association.

Clinical Practice Guidelines

American College of Gastroenterology (ACG)

The ACG published recommendations for the management of patients with hereditary gastrointestinal cancer syndromes, including genetic testing recommendations (Syngal et al., 2015). The authors noted that genetic testing is widely available and should be standard of care for patients at increased risk for a hereditary cancer syndrome. The guidelines recommend targeted gene analysis for the syndrome that is most likely responsible for a patient's symptoms. The authors addressed multigene panels and NGS technology, noting that genetic specialists are increasingly using NGS panels for patients with more than one genetic syndrome on the differential diagnosis list, as testing for multiple conditions at once can decrease costs and be time efficient compared with sequentially screening the possible list of genes. However, it is additionally noted that even though there might be efficiency compared with sequential screening, the time to results is typically longer for large panels. The larger the panel, the more likely it is that VUSs will be found. In addition, the authors caution that these panels often include genes for which there are little data on how to manage cancer risks, and sometimes the degree of cancer risk is unknown. In these situations, the clinician is no better off and must manage the patient based on family and medical history, which can cause confusion for the patient. At the time of publication, the authors did not recommend multiple gene sequencing but noted that in the future, it is likely that at-risk patients may be screened simultaneously for all hereditary cancer syndrome genes.

Collaborative Group of the Americas on Inherited Gastrointestinal Cancer (CGA-IGC)/National Society of Genetic Counselors (NSGC)

In 2022, the CGA-IGC and NSGC published a practice resource addressing genetic evaluation of LS (Holter et al., 2022). The resource indicates that the term "Lynch syndrome" should only be used when patients have been identified to have germline heterozygous P/LP variants in the MMR genes, including *MLH1, MSH2, MSH6,* and *PMS2*, or 3' terminal deletions of *EPCAM*. The following clinical criteria are provided for identifying patients who should be evaluated for LS:

- Patient has a family history of a known germline MMR P/LP variant
- Patient has a personal history of CRC or EC, with any of the following characteristics:
  - Age at diagnosis of less than 50 years
  - Tumor is dMMR: microsatellite instability high or abnormal MMR immunohistochemistry
  - Another LS-related cancer*
  - Family history of LS-related cancers in first- or second-degree relatives
    - At least one relative(s) diagnosed at age < 50 years
    - At least two relatives diagnosed at any age
- Family history of cancer, meeting any of the following criteria:
  - At least one first-degree relative(s) with CRC or EC diagnosed at age < 50 years
  - At least one first-degree relative(s) with at least one diagnosis of LS-related cancers
  - At least two or more first- or second-degree relatives with LS-related cancers, with at least one diagnosed at age < 50 years
  - At least three or more relatives with LS-related cancers at any age
- Genetic risk model score of ≥ 5% predicted probability of germline MMR P/LP variant (e.g., PREMM$_5$, MMRpro)

*LS cancers: colorectal, endometrial, small bowel, urothelial, ovarian, stomach, biliary, pancreatic, sebaceous, and brain.

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines present evidence-based criteria for genetic testing in patients who may have hereditary high-risk CRC/EC syndromes (NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric v1.2025). The guidelines address genetic risk assessment, counseling, testing, and management based on test results and indicate that germline multigene panels are an alternative strategy to tumor- and family history–driven selection of patients with CRC or EC for testing; germline multigene panels have greater sensitivity for identifying patients affected by LS and other cancer risk genes than selecting specific germline testing based on family history or tumor-based criteria. When used, germline

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MGPT should include, at a minimum, the following CRC-related genes: *APC, MUTYH, MLH1, MSH2, MSH6, PMS2, EPCAM, BMPR1A, SMAD4, PTEN, STK11,* and *TP53.* For EC, the following genes should be included in germline MGPT*: MLH1, MSH2, MSH6, PMS2, EPCAM, PTEN,* and *BRCA1/2.* Use of panels that include genes beyond those above should be based on factors such as age at presentation, phenotype of polyps, personal and family history of cancer, and patient/provider preference. The guideline further notes that commercially available multigene tests may differ substantially on the specific genes analyzed by the panel, total number of genes analyzed, and turnaround time, among other things. The NCCN advises that the choice of the specific laboratory/test panel is critical and that multigene testing is ideally offered with professional genetic expertise in cancer genetics, including pre- and posttest counseling.

Lynch Syndrome Testing Criteria

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.

Testing for LS is recommended in the following situations:

- There is a known LS PV in the family
- Patient has LS-related cancer and any of the following:
  - Diagnosed at 49 years or younger
  - Diagnosed with a synchronous or metachronous LS-related cancer at any age
  - Has a first- or second-degree relative with an LS-related cancer diagnosed at 49 years of age or younger
  - Has two or more first- or second-degree relatives with an LS-related cancer, regardless of age
- Patient has a family history of any of the following:
  - One or more first-degree relatives with CRC or EC diagnosed at 49 years of age or younger
  - One or more first- or second-degree relatives with CRC or EC and a synchronous or metachronous LS-related cancer at any age
  - Two or more first- or second-degree relatives with LS-related cancers, including one or more diagnosed at age 49 years or younger
  - Three or more first- or second-degree relatives with LS-related cancers at any age
- Patient has a 5% or greater risk of MMR gene PV based on predictive models (e.g., $PREMM_5$, MMRpro, MMRpredict)
  - Patients with a personal history of CRC and/or EC with a $PREMM_5$ score of 2.5% or greater should be considered for MGPT
  - Patients with no personal history of CRC and/or EC may use a $PREMM_5$ score of ≥ 2.5% rather than ≥ 5% for selection for MMR testing, when used with clinical judgement
- Personal history of a tumor with dMMR, determined by polymerase chain reaction, NGS, or immunohistochemistry, diagnosed at any age
- Personal history of a P/LP variant detected on tumor genomic testing that has clinical implications if also detected in germline testing

Testing may be considered for patients with a personal history of CRC or EC diagnosed at 50 years of age or older, who are untested for dMMR status in a tumor or have a documented absence of dMMR in a tumor.

Adenomatous Polyposis Testing Criteria

Testing is recommended when:

- Patient has a personal history of 20 or more cumulative adenomas
- Family history of a known PV in an adenomatous polyposis gene
- Patient has multifocal/bilateral congenital hypertrophy of retinal pigment epithelium
- Patient has a personal history of a cribriform-morular variant of papillary thyroid cancer
- There is a family history of polyposis, and family is unwilling or unable to undergo testing

In addition, testing may also be considered if a patient has one or more of the following:

- A personal history of a desmoid tumor, hepatoblastoma, or unilateral congenital hypertrophy of retinal pigment epithelium
- Patient meets criteria for serrated polyposis syndrome and has at least some adenomas
- Patient has a personal history of between 10 and 19 cumulative adenomas

For patients with any cancer and a P/LP *APC* variant identified on tumor-only genomic testing, germline testing should be considered for:

- Patients who meet one or more of the other adenomatous testing criteria above after reevaluation of personal and family history

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- Patients diagnosed with any cancer at less than 30 years of age

Age at onset, family history, and/or presence of other features may influence whether genetic testing is offered in some situations.

U.S. Multi-Society Task Force on Colorectal Cancer (USMSTF)

The USMSTF is a group of CRC experts chosen by the American Gastroenterological Association, the ACG, and the American Society for Gastrointestinal Endoscopy and at times includes other experts when needed for additional expertise. In 2022, this group published recommendations for the diagnosis and management of cancer risk in gastrointestinal hamartomatous polyposis syndromes (Boland et al., 2022), including the following regarding genetic evaluation and testing:

- Patients with any of the following should undergo a genetic evaluation: 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. Genetic testing (if indicated) should be performed using MGPT (strong recommendation, low quality of evidence).
- Genetic evaluation should be performed in any patient with the following: (1) two or more histologically confirmed Peutz-Jeghers polyps, (2) any number of Peutz-Jeghers polyps in a patient who has a family history of Peutz-Jeghers syndrome in a first-degree relative, (3) characteristic mucocutaneous pigmentation in a patient with a family history of Peutz-Jeghers syndrome, or (4) any number of Peutz-Jeghers polyps in a patient with the characteristic mucocutaneous pigmentation of Peutz-Jeghers syndrome (strong recommendation, low quality of evidence).
- Genetic evaluation in any patient with (1) five or more juvenile polyps of the colon or rectum, (2) two or more juvenile polyps in other parts of the gastrointestinal tract, or (3) any number of juvenile polyps and one or more first-degree relatives with juvenile polyposis syndrome is recommended (strong recommendation, low quality of evidence).
- The task force suggests that patients with SMAD4 PVs should be clinically evaluated for hemorrhagic telangiectasia at the time of the diagnosis, including screening for and appropriate management of cerebral and pulmonary arteriovenous malformations (weak recommendation, low quality of evidence).
- Patients with multiple gastrointestinal hamartomas or ganglioneuromas should undergo genetic evaluation for Cowden syndrome and related conditions (strong recommendation, low quality of evidence).

Other Cancers or More Than One Hereditary Cancer Syndrome

A 2023 Hayes Precision Medicine Insight found minimal support in the published literature and no/unclear support in the existing published guidelines for the use of multisyndrome panel testing to assist with the clinical management of individuals with a suspected hereditary cancer syndrome. Four clinical studies addressing multisyndrome panel testing were identified, but none compared the use of comprehensive multisyndrome panels with targeted testing or reported clinical outcomes.

In a retrospective review of clinical data and test results from patients with suspected hereditary pheochromocytomas and paragangliomas (PPGLs), Horton et al. (2022) shared the results of MGPT performed using PGLNext (Ambry Genetics, Aliso Viejo, CA) in this group of clinically and ancestrally diverse patients. Existing practice guidelines recommend sequential gene testing strategies determined by individual clinical features; however, the authors indicated that these guidelines were developed prior to the routine availability and use of MGPT. A total of 1,727 patients who received targeted MGPT related to suspicion of hereditary PPGL were included in the review. The analysis revealed that 27.5% of the patients had a P/LP, 9.0% had a VUS, and 63.1% of results were negative. The PVs were most often found in *SDHB* (40.4%), then *SDHD* (21.1%), *SDHA* (10.1%), *VHL* (7.8%), *SDHC* (6.7%), *RET* (3.7%), and *MAX* (3.6%). Patients with extra-adrenal location of disease, early age at onset, a positive family history of PPGL, and multiple tumors were most likely to have PVs (85.9%). Per the results of this study, limiting genetic tests to *SDHB/C/D* would result in only missing approximately one-third (32.8%) of patients with PVs. Overall, the researchers concluded that the data from this study indicate a high diagnostic yield in patients with or without known risk factors, significant contribution to diagnostic yield from rare genes, and low rate of inconclusive results, which supports the use of universal testing with MGPT for all individuals with PPGL, regardless of tumor type, age at onset, metastatic disease, syndromic features, family history, and functional status.

Nölting et al. (2022) published a review integrating current guidelines and expert opinions regarding the personalized management of PPGLs. PPGLs have the highest rate of heritability among all tumors, with approximately 30% to 35% of Caucasian individuals (lesser percentage in the Chinese population) showing germline mutations. In addition, 35% to 40% of Caucasian individuals (higher in the Chinese population) have an impact from somatic driver mutations. The article asserts that accurate genetic testing in these individuals is indispensable and recommends such testing for every affected individual because identification of the molecular cluster associated with the PPGL [pseudohypoxia cluster 1 (1A and 1B), kinase-signaling cluster 2, and Wnt signaling cluster 3] has been shown to positively impact management and overall

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outcomes. The preferred testing technique is NGS so that all important genetic variations can be identified via one single test.

Uson et al. (2021) documented the results of a prospective multisite study that used an NGS panel with greater than 80 genes to perform germline sequencing in 250 participants with pancreatic cancer. Included participants were not selected for a family history of cancer or age. Pathogenic germline variants (PGVs) were found in 15.2% of participants, with two participants testing positive for more than one PGV. VUSs were found in 44.4% of participants. Participants with a family history of cancer were associated with a higher risk of PGV. Overall, 68% of PGV carriers had mutations in *BRCA1, BRCA2, PALB2, ATM, CHEK2, NBN*, and *RAD51C*. The most common PGVs were found in *BRCA2* (22.5%), *ATM* (17.5%), and *CHEK2* (10%). Overall, in this study, one in six participants with pancreatic cancer was a carrier of a PGV. The authors recommended that multigene germline testing should be used in individuals with pancreatic cancer to aid in selection of treatment, prognostication, and counseling of family members regarding risk.

In a 2021 publication, Samadder et al. (included in the Hayes 2023 Precision Medicine Insight report discussed above) reported on a prospective, multicenter cohort study examining the prevalence of PGVs in participants with cancer using a universal approach rather than targeted testing based on clinical practice guidelines. A total of 2,984 participants with solid tumor cancers were studied. Participants were not selected based on cancer type, disease state, family history, age, or ethnicity. Germline sequencing using NGS with greater than 80 genes was provided to the participants. The researchers were looking to compare this universal strategy with the standard guideline-directed approach and assess the uptake of cascade family variant testing. PGVs were detected in 397 participants (13.3%), and 1,415 participants (47.4%) were found to have a VUS. Clinically actionable findings that would not have been detected by family history or phenotype-based testing criteria were identified in 192 participants. Of those with high-penetrance PGV, modifications in treatment were made in 42 study participants. A younger age at diagnosis (mean age, 61.4 years) was associated with the presence of PVG, and only 17.6% of participants (n = 70) with PGVs had members of their family undergoing family variant testing. The authors concluded that the universal MGPT in participants with a solid tumor cancer was associated with a higher rate of detection of heritable variants than the predicted yield of guideline-based targeted testing in this study. Despite the testing being free to family members, the uptake of cascade family variant testing was low. Noted limitations include the lack of long-term follow-up for assessment of cancer-related deaths and morbidity related to prophylactic surgery, targeted therapy, or preventative screening. Additionally, guidelines addressing family history and the need for testing used by the expert reviewers for the study underwent a change during the study, which may have impacted the outcome. Lastly, the demographics among participants in this study may not mirror those in other regions, which may limit generalization to other populations.

LaDuca et al. (2020) evaluated 32 cancer predisposition genes to study the effect of MGPT on hereditary cancers. The cohort consisted of 165,000 individuals referred for MGPT, and the researchers assessed phenotype-specific PV frequencies, cancer risk associations, and performance of genetic testing criteria. The study identified extensive genetic heterogeneity, with the predisposition to cancer types commonly referred for germline testing (breast, ovarian, colorectal, uterine/endometrial, pancreatic, and melanoma). Individuals with ovarian cancer had the highest PV frequencies (13.8%). Fewer than half of the PVs identified were in individuals who met the testing criteria for only *BRCA1/2* (33.1%) or only LS (46.2%). Among individuals who did not meet the testing criteria, 5.8% had PVs in *BRCA1/2*, and 26.9% had PVs in LS genes.

Muth et al. (2019) discussed PPGLs, which are rare tumors stemming from the chromaffin cells in the adrenal medulla (pheochromocytoma) or the sympathetic or parasympathetic extra-adrenal paraganglia (paraganglioma), in their publication of genetic testing and surveillance guidelines related to the management of these conditions in affected individuals and their family members. The authors indicated that at least 30% of PPGLs are part of hereditary syndromes, and approximately 20% of hereditary PPGLs are caused by PGVs in genes of the succinate dehydrogenase complex, *TMEM127* or *MAX*. They stated that at a minimum, testing for *FH, NF1, RET, SDHB, SDHD*, and *VHL* in individuals with PPGL should be done but also recommended testing for *MEN1, SDHA, SDHAF2, SDHC,TMEM127*, and *MAX*. First-degree relatives (and second-degree relatives for *SDHD* and *SDHAF2*, which are maternally imprinted) should be offered carrier testing.

In a study by Gardner et al. (2018), 630 individuals (84% of whom had a family history of cancer) were tested with a 27-gene inherited cancer panel. Of these individuals, 65 were determined to have variants classified as P/LP across 14 genes (10.3%). Only 42% of these variants occurred in classic HBOC- or LS-associated genes, while 58% were observed in high- or moderate- to low-risk genes on the panel. The researchers concluded that there is utility in using multigene panels over single-gene testing, particularly in those with an inherited predisposition to cancer.

Rednam et al. (2017) discussed the genes related to hereditary PPGL syndrome in their 2017 publication on Von Hippel-Lindau and hereditary PPGL syndrome. Genes related to hereditary PPGL include the succinate dehydrogenase complex

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genes, *MAX and TMEM127*, and potentially *HIF2α EGLN1* and *KIF1β* as well as genes that are components of other hereditary tumor predisposition syndromes, including *RET, VHL, NF1*, and *FH*. The authors noted that up to 35% of PPGLs are hereditary, and diagnosis is based on molecular genetic testing that should be offered to any affected individual.

An analysis of 252,223 participants (most of whom were suspected to have HBOC or LS) was performed by Rosenthal et al. (2017) using a 25-gene pan-cancer panel. Of these participants, the majority (92.8%) met the testing criteria for HBOC and/or LS. PVs were identified in 6.7% of the tested participants, with the most commonly identified PVs found in *BRCA1/2* (42.2%), other breast cancer genes (32.9%), and LS genes (13.2%). However, half of the PVs in participants who met only HBOC criteria were in non-*BRCA1/2* genes. Likewise, in participants who met LS criteria, half of the PVs identified were in non-LS genes. These researchers suggested that a pan-cancer panel may provide improved identification of PVs over single-syndrome testing.

Bholah and Bunchman (2017) published a review of the literature regarding PPGL, in which they demonstrated that the generally accepted estimate of 10% of cancers being hereditary may not apply to PPGL. They noted that the European-American-Pheochromocytoma-Paraganglioma-Registry has released data showing that 80% of individuals in their registry had a germline mutation compared with previous smaller pediatric case series that estimated a germline mutation prevalence of 30% to 40%. Genes that are involved in PPGL include genes associated with known neuroendocrine syndromes such as von Hippel-Lindau (*VHL*), multiple endocrine neoplasia type II (*RET*), and neurofibromatosis I (*NF1*) as well as mitochondrial-related genes. These include the subunits for succinate dehydrogenase, *SDHA, SDHB, SDHC, SDHD,* and *SDHAF2*, and the *TMEM, HIPF2A*, and *MAX* genes. Variants in these genes can cause rare autosomal dominant PPGL syndromes, with varying penetrance.

A retrospective study by Babic et al. (2017) analyzed pediatric PPGLs to determine the role of genetic testing. Of 55 pediatric patients, 44 (80%) had a germline mutation, with the majority found to have either a *VHL* (38%) or *SDHB* (25%) mutation. The authors concluded that the majority of pediatric individuals with PPGL likely have detectable germline mutations; therefore, genetic testing may be helpful to guide treatment.

Nguyen et al. (2017) published a retrospective review of the use of a 19-gene hereditary cancer panel in patients diagnosed with kidney cancer. Patients were tested at a commercial laboratory from August 2013 to June 2016. Clinical characteristics such as age, gender, age at diagnosis, ordering institution, kidney cancer histology, personal history, and cancer history were obtained from test requisitions. In total, 1,235 patients with renal cell carcinoma had testing. The majority of the cohort was Caucasian (64%) and male (54%). The average age at diagnosis was 46 years. Histology was available for 942 patients, and common tumor histology such as clear cell, papillary, and chromophobe kidney tumors was present in 67% of them. The remainder reported less common and mixed histology. Overall, 859 had only kidney cancer, 283 had an additional primary cancer, and 93 had more than two primary cancers. A positive family history of cancer was reported in 1,007 patients, and of them, 369 reported a family history of kidney cancer. Half of all cases were referred by university-based hospitals, 44% were referred from non-university hospitals, and 4.5% came from private practice clinicians. Genetics providers referred 81% of cases, oncologists referred 14%, nononcology physicians referred 1%, and other health care providers referred the remainder. Overall, 6.1% had a PV identified, 18% had a VUS, and the remainder had a negative result. Mutations were found in 15 of the 19 genes in the panel. The genes with the highest rate of mutations were *FLCN, FH, MITF*, and *SDHB*. The authors noted that their study was limited by the retrospective review and the reliance on submitted histology information and not a centralized pathology review. It was additionally noted that panel tests are relatively new, and the larger the panel, the more likely that VUSs are found. The outcomes and decisions by treating physicians were not available, but it has been hypothesized that clinicians may act and medically intervene for VUSs when it may not be warranted. However, this is the first publication to report on the results in a large cohort of patients with kidney cancer undergoing multigene hereditary cancer panel testing.

Clinical Practice Guidelines

American Society of Clinical Oncology (ASCO)

An ASCO multidisciplinary panel of experts developed recommendations guiding the use of germline multigene panels for patients with cancer in 2024. The recommendations were based on a systematic review of 52 existing guidelines and consensus statements and 14 studies addressing germline and somatic genetic testing in a wide spectrum of diseases; the recommendations were published as an ASCO guideline (Tung et al., 2024). The summarized recommendations are as follows:

- All patients with cancer should have a comprehensive family history taken and recorded (evidence quality: not rated; strength of recommendation: strong).
- When indicated, germline testing using a multigene panel should be offered to patients diagnosed with cancer if more than one relevant gene is present (evidence quality: not rated; strength of recommendation: strong).

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- The panel should, at a minimum, include at least the more strongly recommended genes for the patient, based on a personal and family history of cancer, and may include less strongly recommended genes as well.
- When benefits can be clearly identified, a broader panel may be ordered; the ordering clinician should ensure that any potential harms from uncertain results are mitigated.
- Smaller gene panels should be applied initially if results are needed quickly for treatment decision-making; larger panels can then be ordered later.

- If germline testing is offered, the genes in the following table are recommended for inclusion in multigene panels for the indicated population of patients with cancer. In addition, because of the importance and prevalence of *BRCA1, BRCA2*, and the LS genes *MLH1, MLH2, MSH6, PMS2*, and *EPCAM*, it is reasonable to use panels that include these genes for any patient with cancer undergoing germline genetic testing (evidence quality: not rated; strength of recommendation: strong).

Cancer Type	More Strongly Recommended	Less Strongly Recommended
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	*EGFR, STK11*	*TP53*
Adrenocortical tumors	*APC, EPCAM, MEN1, MLH1, MSH2, MSH6, PMS2, TP53*	NA
Cutaneous melanoma	*CDKN2A, CDK4*	*BAP1, MC1R, MITF, POT1, TERT, PTEN*
Uveal melanoma	*BAP1*	NA
Epithelial ovarian cancer	*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*
Pheochromocytomas 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	*TP53*	*NF1, RB1*

- When a patient meets the criteria for germline testing, it should be offered, regardless of the results of tumor testing (evidence quality: low; strength of recommendation: strong).
- When tumor testing reveals a PV in *BRCA1, BRCA2, BRIP1, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, RAD51C, RAD51D, RET, SDHAF2, SDHB, SDHC, SDHD, TMEM127, TSC2,* or *VHL,* and only if the patient is < 30 years of age, *APC, PTEN, RB1*, and *TP53*, germline genetic testing should be offered regardless of germline genetic

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testing criteria. When tumor testing indicates a PV in *ATM, BAP1, BARD1, CHEK2, DICER1, FH, FLCN, NF1, POLD1, POLE,* or *SDHA* and, only if the patient is < 30 years of age, *CDKN2A* and *SMARCA4*, germline genetic testing may also be offered, unless a more conservative approach is desired. If a conservative approach is preferable, testing for these genes may be limited to patients with the gene/relevant tumor types in the table below (evidence quality: moderate; strength of recommendation: strong).

Gene	Relevant Tumor Types
ATM	Breast cancer, gastric cancer, epithelial ovarian cancer, pancreatic adenocarcinoma, prostate cancer
BAP1	Melanoma, renal cell carcinoma, malignant mesothelioma
BARD1	Breast cancer
CDKN2A	Melanoma or pancreatic adenocarcinoma
CHEK2	Breast cancer, colon cancer, prostate cancer, thyroid cancer
CHEK2	c.1100del testing should occur regardless of tumor type
DICER1	*DICER1* pleuropulmonary blastoma, cystic nephroma, embryonal rhabdomyosarcoma, ovarian Sertoli-Leydig cell tumors, ovarian sarcoma, neuroblastoma, thyroid cancer
FH	Paraganglioma, pheochromocytoma, renal cell carcinoma
FLCN	Renal cell carcinoma
NF1	Breast cancer, gastrointestinal stromal tumor, paraganglioma, pheochromocytoma
POLD1	Colorectal cancer
POLE	Colorectal cancer
SDHA	Gastrointestinal stromal tumor, paraganglioma, renal cell carcinoma
SMARCA4	Small cell carcinoma of ovary, hypercalcemic type and malignant rhabdoid tumors

In addition to the recommendations above, the importance of accessible genetic counseling services is underscored in the 2024 ASCO guideline, noting that genetic expertise is required to interpret the results of tests outlined in this guideline, especially as the number of genes included in multigene panels increases. Additionally, for families in which PVs are identified, the facilitation of cascade testing and support services will require assistance from genetic counselors or other genetic experts. Finally, the ASCO expert panel notes that although large germline testing panels are becoming more common, it is important to balance the benefits vs harms of these panels; broad panels may detect important PVs, but without appropriate interpretation of results, unnecessary anxiety or even inappropriate prevention practices and/or screening could occur.

Stoffel et al. (2019) published a provisional clinical opinion resulting from ASCO's expert panel literature review on pancreatic cancer. Several sections regarding genetic testing were present in Research Question 2: "Which individuals should undergo genetic testing for predisposition to pancreatic cancer?". The provisional clinical opinion indicates that all individuals with PAC should undergo risk assessment for those hereditary cancer syndromes that are associated with pancreatic cancer. Testing and assessment of risk should include a review of a family history of cancer. The opinion also stated that germline genetic testing for cancer susceptibility should be considered in those with pancreatic cancer and an unremarkable family history.

Genetic testing for cancer susceptibility may be efficient in circumstances in which the medical and family history of an individual requires evaluation of multiple high-penetrance genes that have established clinical utility. Because such panels might include genes with low to moderate penetrance and results could include VUSs, it is recommended that providers with particular expertise in cancer risk assessment be involved in the ordering and interpretation of MGPTs, especially those that include genes of uncertain clinical utility and genes not suggested by the individual's personal and/or family history (Robson et al., 2015).

National Comprehensive Cancer Network (NCCN)

Prostate Cancer

The NCCN Practice Guidelines for Prostate Cancer (v2.2026) directs the user to the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate cancer and the NCCN Guidelines for Genetic/Familial High Risk Assessment: Colorectal, Endometrial, and Gastric cancer and indicate that the criteria in those guidelines should be referenced at the time of initial diagnosis of prostate cancer, and if applicable, at recurrence. Germline testing should be considered in appropriate candidates for whom the information obtained could impact prostate

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cancer treatment and/or clinical trial options, management of risk for other cancers, and potential risk in family members. If criteria in the guidelines that are referenced above are met, germline multigene testing should include at least *BRCA1, BRCA2, ATM, PALB2, CHEK2, HOXB13, MLH1, MSH2, MSH6*, and *PMS2*. In addition, patients with prostate cancer undergoing tumor molecular analysis should be counseled that tumor testing using DNA sequencing may reveal germline findings as well.

Pancreatic Adenocarcinoma

The NCCN Clinical Practice Guidelines for Pancreatic Adenocarcinoma (v2.2025) recommend germline genetic testing using comprehensive gene panels for hereditary cancer in any patient with confirmed pancreatic cancer and those in whom there is a clinical suspicion for heritable susceptibility. The guideline directs the user to the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate cancer and the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric cancer (for pancreatic cancer in LS). Genetic counseling is recommended in patients with pancreatic cancer who test positive for a pathogenic mutation (*ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, PALB2, PMS2, STK11*, or *TP53*) or have a positive family history of cancer, especially pancreatic cancer, regardless of mutation status.

Neuroendocrine and Adrenal Tumors

The NCCN Clinical Practice Guidelines for Neuroendocrine and Adrenal Tumors (v2.2024) address genetic counseling and testing for patients with neuroendocrine tumors (NETs) and note that the introduction of multigene genetic testing for hereditary endocrine neoplasias has quickly changed the clinical approach to genetic testing in these patients. Because of the potential overlap in various heritable endocrine neoplasias, it is suggested that multigene testing may have greater efficiency in many situations. Genes associated with hereditary endocrine neoplasia syndromes include *MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127, MEN1, RET, CDKN1B, NF1, TSC1, TSC2,* and *VHL*. Hereditary cancer predisposition syndromes associated with adrenocortical carcinoma include Li-Fraumeni (*TP53*), LS (*MLH1, EPCAM/MSH2, MSH6,* and *PMS2*), multiple endocrine neoplasia (*MEN1*), and familial adenomatous polyposis (*APC*). However, the interpretation of genetic testing in these conditions can be complex and subjective. Per the v2.2024 guideline, genetic risk evaluation and testing for hereditary endocrine neoplasia syndromes are recommended for patients who meet any of the following criteria:

- Patient has adrenocortical carcinoma
- Patient has pheochromocytomas or paragangliomas
- Patient has a parathyroid adenoma or primary hyperparathyroidism prior to 30 years of age, has multiple parathyroid adenomas, has multigland hyperplasia (without an obvious secondary cause), or has recurrent primary hyperparathyroidism
- There is clinical suspicion of MEN2 due to medullary thyroid carcinoma or other combination of MEN2-related characteristics
- There is a clinical suspicion of MEN1 due to two or more of the following or one of the following and a family history of one or more of the following:
  - Primary hyperparathyroidism
  - Duodenal/pancreatic NET
  - Pituitary adenoma
  - Foregut carcinoid (lung, thymic, or gastric)
- A mutation was identified on tumor genomic testing that has clinical implications if identified in the germline
- A close blood relative has a known P/LP variant in a cancer susceptibility gene
- A first-degree relative has met one of the criteria above but is not available for testing

Genetic testing and risk evaluation may be considered for the following:

- Patient has gastrinoma (duodenal/pancreatic or type 2 gastric NET)
- Patient has multifocal PanNETs
- Patient has a duodenal/pancreatic NET at any age
- There are other combinations of tumors or cancers in the patient and/or their family members

Kidney Cancer

The NCCN's v1.2026 Clinical Practice Guidelines for Kidney Cancer address the use of genetic risk evaluation for patients with renal cell carcinoma, noting that use of a kidney cancer–focused multigene panel or clinically directed single-gene testing should be considered for patients with clinical features of hereditary renal cell carcinoma. Specific recommendations include the following:

- Genetic risk evaluation and testing, if indicated, should be performed in the following situations:
  - Patient has a close blood relative with a known P/LP variant in a cancer susceptibility gene

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- Patient has renal cell carcinoma and any of the following:
  - Diagnosed at 46 years of age or younger
  - Diagnosed at any age with bilateral or multifocal tumors
  - Has one or more first- or second-degree relatives with renal cell carcinoma
  - Has a personal or family history of mesothelioma or uveal melanoma
- Patient has renal cell carcinoma and tumors have the following histological characteristics:
  - Multifocal papillary histology
  - Hereditary leiomyomatosis and renal cell cancer-associated renal cell carcinoma, renal cell carcinoma with fumarate hydratase deficiency, or other histological features associated with hereditary leiomyomatosis and renal cell cancer
  - Birt-Hogg-Dubé syndrome–related histology
  - Angiomyolipomas of the kidney and one additional tuberous sclerosis complex criterion in the same patient
  - Succinate dehydrogenase–deficient renal cell carcinoma histology
- Patient is unaffected but has the following family history:
  - Two or more first- or second-degree relatives on the same side of the family with renal cell carcinoma
  - First-degree relative meeting criteria for genetic evaluation for renal cell carcinoma but is unwilling/unable to undergo genetic testing

Polygenic Risk Scores

A polygenic risk score (PRS) is an evaluation of the risk of a specific condition based on the combined effect of many different genetic variants. PRSs may include variants that are related to genes of known function and variants that have no known association with genes pertinent to a particular condition or disease (NCI Dictionary of Genetics Terms, 2024). Evidence to support the use of PRS for assessing hereditary cancer risk is currently insufficient.

Timbres et al. (2025) investigated the relationship between PRS for breast cancer and outcomes following in situ breast disease, specifically ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS) in a retrospective cohort study. The researchers sought to determine whether a higher genetic predisposition to breast cancer, as measured by PRS, correlated with an increased risk of subsequent invasive breast cancer or other adverse outcomes. Using data from a large cohort of women in the ICICLE (Investigate the Genetics of In Situ Carcinoma of the Ductal Subtype) and GLACIER (Genetics of Lobular Carcinoma In Situ in Europe) studies with DCIS (n = 2,169) or LCIS (n = 185), the authors calculated PRS based on known breast cancer–associated genetic variants. They then tracked outcomes including further in situ or invasive breast cancer, whether ipsilateral, contralateral, or distant metastases. The results revealed that a higher PRS was significantly associated with an increased risk of developing contralateral disease (both in situ and invasive) after DCIS as well as a suggested relationship between PRS and ipsilateral disease following LCIS. The authors proposed that PRS could be a useful tool in risk stratification, helping clinicians identify which individuals might benefit from more aggressive surveillance or preventive strategies. However, the study was not without limitations. There was a lack of ethnic/racial diversity, which may limit the generalizability of PRS use across broader populations, and other potentially influential clinical factors, such as hormone receptor status and lifestyle factors, were not fully incorporated. In addition, the number of LCIS samples was small. The analysis was done by extending the original ICICLE and GLACIER case-control studies into one cohort via the use of follow-up data; some cases were omitted from the follow-up data due to lack of consent, which may have introduced selection bias. Although this study suggests that the use of PRS could be helpful to identify individuals at a higher risk for second primary cancers following in situ disease, further high-quality studies are required to validate this finding.

Using a combined analysis of two prospective cohort studies [Malmö Diet and Cancer Study (MDCS) in Sweden; Health Professionals Follow-Up Study (HPFS) in the United States], Plym et al. (2024) investigated the differences in the risk of early prostate cancer death in men with higher vs lower genetic risk. A combination of modifiable lifestyle behaviors and genetic risk was used to categorize study participants, with a PRS above the median or a family history of cancer defining participants at higher genetic risk. Participants who did not meet these criteria (33%) were categorized as lower risk. A total of 19,607 men were included in the evaluation, with a median age of 59 years in MDCS and 65.1 years in HPFS. A total of 107 deaths by age 75 years and 337 deaths after age 75 years occurred due to prostate cancer. Those participants with a higher genetic risk, as assessed by a PRS that included 400 genetic risk variants and/or a family history that included at least one first-degree relative with any cancer or prostate/breast cancer, had increased rates of both early and late prostate cancer death (hazard ratio, 3.26, 95% CI, 1.82-5.84 and hazard ratio, 2.26, 95% CI, 1.70-3.01, respectively) as well as overall higher lifetime risks of death due to prostate cancer [3.1% vs 1.3% (MDCS) and 2.3% vs 0.6% (HPFS)]. Of the total early prostate cancer deaths, men at a higher genetic risk made up 88% (94/107); cases in 36% of those men (95% CI, 12%-60%) were projected to be preventable through behaviors such as maintaining a healthy weight, refraining from smoking, maximizing physical activity, and consuming a healthy diet. The authors concluded that the results from this 20-year follow-up study suggest that men with the genetic predisposition for prostate cancer make up the large majority of individuals with early prostate cancer death and should receive focused attention for

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prostate cancer prevention tactics. Noted limitations include the lack of randomization and assessment of factors only at entry into the study. Participants were limited to men of European ancestry, and differences in prostate cancer testing and treatment could account for some of the association between healthy lifestyle and prostate cancer death. Further studies that better define appropriate screening technology for genetic risk as well as the impact of targeted interventions related to genetic results are required.

In a 2023 systematic review and meta-analysis, Siltari et al. (2023) analyzed the existing evidence addressing the use of PRS as a predictor of prostate cancer in Caucasian men. A total of 59 studies were included in the assessment, with 16 studies and 17 separate analyses used in the primary meta-analysis. In all, 20,786 cases and 69,106 controls were identified. The researchers found that the ability of PRS to detect men with prostate cancer was modest [pooled area under the curve (AUC), 0.63; 95% CI, 0.62-0.64] and had moderate consistency (I^2, 64%). When PRS was combined with clinical variables, the pooled AUC increased to 0.74 (0.68-0.81). A very limited increase in AUC was demonstrated when incremental single-nucleotide polymorphism (SNP) assessments were added. Overall, the authors interpreted these findings to indicate that PRS accuracy is comparable to that of prostate-specific antigen testing and family history and noted that the optimal method for calculating PRS is unclear.

Mbuya-Bienge et al. performed a critical assessment of the use of PRS generated by SNPs to help predict breast cancer risk in the general population through a 2023 systematic review. Included studies described the development or validation of a breast cancer risk prediction model using a PRS and reported a measure of predictive performance. Studies that incorporated individuals with a history of breast cancer and/or known genetic risk or those that focused on any specific population were excluded. A total of 37 articles (29 of which used both genetic and nongenetic risk factors) exploring seven different risk prediction tools were reviewed. The majority of the models (55%) were created based on populations of European ancestry; these generally performed better than models developed based on other ancestry groups. Overall, models that combined PRS with both genetic and nongenetic risk factors had better discriminatory accuracy (AUC from 0.52-0.77) than those models that used PRS alone (AUC from 0.48-0.68), irrespective of the number of SNPs in the PRS. Based on these results, the authors concluded that breast cancer risk prediction models that combine PRS with genetic and nongenetic risk factors appear to be the most accurate, but additional study is required to better understand how these tools may be refined and applied in clinical practice.

Clinical Practice Guidelines

American College of Medical Genetics and Genomics (ACMG)

A 2023 ACMG statement (Abu-El-Haija et al.) addressed the clinical application of PRS, citing several points to consider regarding the use of this technology, given the limited evidence of clinical utility at this time. The document highlights that a low PRS does not rule out a significant risk of the disease/condition in question and could have poor predictive value if the patient considered for testing is from a different population than that from which the PRS was derived. In addition, isolated PRS testing for clinical situations in which there is a suspected/known monogenic etiology is not appropriate. Medical management based on PRS results should be evidence based; however, at present, limited evidence exists to support the use of PRS to guide intervention. It is important that patients who are considering PRS have a discussion with their provider or counselor about test limitations and information regarding how PRS results may guide clinical management. Such management should be consistent with the best practices documented in evidence-based professional society guidelines, with applicable expertise (when such guidelines exist). Overall, the ACMG does not support the clinical implementation of PRS tools, unless the provider and the patient under consideration for such testing have a thorough understanding of the limitations of PRSs and how individual results may be used to guide appropriate clinical care.

Genetic Testing of *BRCA1/2* or Multigene Hereditary Cancer Panels With RNA Testing

There is insufficient evidence to support the use of concurrent RNA panel testing as part of genetic testing of *BRCA1/2* or in multigene hereditary cancer panels. The quality of existing studies is low due to small study populations, short follow-up times, and a lack of randomization and appropriate control groups. While RNA testing may clarify certain variants identified from DNA testing, more high-quality studies are needed before RNA panels are broadly used.

A recent study by Landrith et al. (2020) reported on a collaboration between Ambry Genetics and 19 other clinical institutions. The researchers evaluated 18 tumor suppressor genes in 345 samples from healthy donors to develop splicing profiles. They then assessed the utility of this splicing profile in 1,000 participants with suspected hereditary cancer syndromes. The RNA testing coupled with DNA testing was performed, and the RNA testing identified seven participants with PVs that would have been negative or inconclusive with DNA testing alone. For six of the seven, medical management changes would likely be recommended. This analysis showed a 9.1% relative increase in diagnostic yield when RNA testing was performed, although the study did not clarify what proportion of variants received new classification

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or confirmation from RNA testing and what proportion was only detected from using a concurrent RNA panel. Further studies are required to aid in the development of standards for interpretation of findings associated with RNA testing.

Karam et al. (2019) evaluated individuals with inconclusive variants in genes known to be associated with HBOC, LS, and hereditary diffuse gastric cancer after DNA testing to determine if RNA testing improved the data. Only 93 of 909 eligible families submitted samples for RNA testing. The RNA testing results clarified the interpretation of 49 of the 56 inconclusive cases (88%) studied. However, only 26 (47%) were reclassified as clinically actionable, and the remaining 23 (41%) were clarified as benign. An additional section of this study evaluated 307,812 results from individuals who had undergone only DNA testing; the researchers determined that 7,265 of them had inconclusive variants that affect splicing. The authors concluded that approximately one in 43 individuals could potentially benefit from RNA testing if it is performed in every individual who is undergoing genetic assessment for hereditary cancer. The researchers highlighted several limitations, including individuals' availability to submit additional blood samples for RNA genetic testing and limited medical management data due to the number of surveys completed. Studies that include the clinical impact of concurrent RNA/DNA genetic testing are needed to provide a full assessment of the potential impact of RNA panel testing.

Whole-Exome Sequencing for Hereditary Cancer Risk Assessment

To determine whether germline genetic screening using exome sequencing technology can efficiently identify carriers of HBOC and LS, Samadder et al. (2024) analyzed participants in the ongoing Tapestry study (ClinicalTrials.gov identifier: NCT05212428). Tapestry is a health study that is investigating the necessary processes for large-scale genomic sequencing and dissemination of results for Centers for Disease Control and Prevention Tier 1 heritable conditions (HBOC, LS, and familial hypercholesterolemia) as well as evaluating downstream clinical impact. Samadder and colleagues focused on participants who had undergone Exome+ sequencing (Helix Inc., San Mateo, CA) for specific results suggesting HBOC (*BRCA1/2*) and LS (*MLH1, MSH2, MSH6, PMS2*, and *EPCAM*) and performed a corresponding chart review to compile demographics as well as participants' personal and family history of cancer. Of the 44,306 Tapestry enrollees with Exome+ results/interpretation at the time of evaluation, 1.24% (n = 550) were carriers for either HBOC or LS genes, including 387 HBOC gene carriers (27.2% *BRCA1*; 42.8% *BRCA2*) and 163 LS gene carriers (12.3% *MSH6*; 8.8% *PMS2*; 4.5% *MLH1*; 3.8% *MSH2*; 0.2% *EPCAM*). Over half of the 550 carriers identified were newly diagnosed as carriers. Notably, 39.2% of all HBOC and LS gene carriers did not meet the NCCN criteria for genetic testing; additionally, these criteria were more infrequently met in underrepresented minority populations than in populations that self-identified as White (51.5% vs 37.5%; p = 0.028). The authors concluded that their findings from this multisite, prospective cohort study underscore the need for broader use of germline testing for improved screening/detection in individuals affected by HBOC and LS cancer predisposition syndromes. The study results indicated that screening via Exome+ could potentially detect approximately 50% of Centers for Disease Control and Prevention Tier 1 condition carriers who would otherwise not be identified based on current processes. However, several limitations have been identified, including the lack of language options for completion of the electronic interface with Helix Labs (only English was available), leading to underrepresentation of minority populations. In addition, the exome sequencing identified carriers of only small P/LP variations such as single-nucleotide variants and small indels, which led to some false-negative results due to the lack of detection of copy number variants that are estimated to be pathogenic in 5% to 25% of HBOC/LS mutation carriers. Lastly, some of the authors had affiliations with laboratories that manufacture genetic tests, including the Exome+ test used in this study. Further high-quality studies that evaluate the best approaches for population-based genetic screening are needed before such screening can be adopted as standard practice.

Van Tung et al. (2025) published the results of an observational study using whole-exome sequencing (WES) to identify genetic variants in a total of 155 Vietnamese women; 105 of the women had breast cancer, and the remaining 50 were healthy. Franklin prediction software and criteria from the ACMG and ClinVar were used to screen for breast cancer–associated variants. Further analysis within silico prediction software was used to predict pathogenicity in the cases of VUSs. Overall, 56 variants in 37 genes were identified in 41 of 105 participants with breast cancer. Of the 56 variants, 43 were determined to be pathogenic; 10 of these were deemed P/LP per ACMG/ClinVar criteria, and the remaining 33 were predicted to be pathogenic via the in silico software. Noteworthy study limitations related to the WES method include the potential omission of variants located in noncoding regions, copy number variants, and large genomic rearrangements associated with breast cancer and lack of comprehensive interpretation of variant effects, particularly in cases in which participants carried multiple variants. In addition, the sample size was small, limiting statistical power, and all participants were Vietnamese, which impacts the ability to generalize findings to broader populations. There was no long-term follow-up; the impact of the identified variants on factors such as disease progression or survival over time was not assessed. Despite these limitations, the authors concluded that WES is a promising tool for detecting breast cancer–associated genetic variants in Vietnamese individuals, including novel and pathogenic mutations, which can inform risk prediction and personalized treatment strategies.

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U.S. Food and Drug Administration (FDA)

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Laboratories that perform genetic tests are regulated under the Clinical Laboratory Improvement Amendments Act of 1988. More information is available at: https://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124105.htm. (Accessed September 19, 2025)

A list of nucleic acid–based tests that have been cleared or approved by the FDA Center for Devices and Radiological Health is available at: https://www.fda.gov/medical-devices/in-vitro-diagnostics/nucleic-acid-based-tests. (Accessed September 19, 2025)

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Policy History/Revision Information

Date	Summary of Changes
10/01/2026	**Applicable Codes** • Updated list of applicable CPT codes to reflect quarterly edits; added 0678U and 0679U **Supporting Information** • Archived previous policy version 2026T0009UU

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its policies and guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

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