Genetic Testing for Hereditary Cancer

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➲ Instructions for Use

Table of Contents **Page**

Related Commercial 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 in all states except for Colorado.

Coverage Rationale

Pre-test genetic counseling is strongly recommended in order 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 is 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 or younger.**

Genetic testing with a Multi-Gene 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 are met:

- Individual has a personal history of at least one of the following:
  - Breast Cancer diagnosed at age 50 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

- Ovarian Cancer (including fallopian tube cancer and/or primary peritoneal cancer)
- Pancreatic cancer
- Metastatic prostate cancer
- Cancer Associated with Lynch syndrome
- Neuroendocrine tumor (e.g., adrenocortical carcinoma, paraganglioma, pheochromocytoma)
- Malignant phyllodes tumors
- 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 history of a Cancer Associated with Lynch Syndrome
  - At least one Close Blood Relative diagnosed with a Primary Solid Tumor (excluding basal or squamous cell skin cancer) at age 40 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,* and *TP53*)
  - Tumor tissue testing demonstrated that the cancer was MSI-high or had immunohistochemical staining showing the absence of one or more mismatch repair (MMR) proteins (*MLH1, MSH2, MSH6,* or *PMS2*)
  - Individual has a Tyrer-Cuzick, BRCAPro, or Penn11 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 Multi-Gene 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 are 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)
  - Cancer Associated with Lynch Syndrome
  - 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 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
- At least one second-degree relative with a history of at least one of the following:
  - Two or more Cancers Associated with Lynch Syndrome
  - Cancer Associated with Lynch Syndrome diagnosed at age 50 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 Cancer Associated with Lynch Syndrome
  - 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 ten cumulative adenomas) for a polyposis syndrome and affected family member(s) is unwilling/unable to have genetic testing

  or
- A personal history of colorectal polyposis with at least ten adenomas; or
- Any of the following:

- Individual has a Tyrer-Cuzick, BRCAPro, or Penn11 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 Multi-Gene hereditary cancer Panel for individuals diagnosed with cancer at age 18 or younger is proven and medically necessary.

Multi-Gene 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.

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 protocol titled Medical Records Documentation Used for Reviews.

Definitions

Age Guidelines: For the statements that include Age Guidelines, a person is considered to be 45 years of age up until the day before their 46th birthday, and a person is considered to be 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 cancer, or prostate cancer [National Comprehensive Cancer Network (NCCN), Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic v1.2025].

Breast Cancer: Either invasive carcinomas or non-invasive (in situ) ductal carcinoma types (NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic v1.2025).

Close Blood Relatives: Defined as follows (NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic v1.2025):
- 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.
- Third-degree relatives include first cousins, great-aunts/uncles, great-grandchildren, and great grandparents affected on same side of 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, 2024; NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic v1.2025].

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 the cancer tissue is similar to normal prostate tissue and the tumor is less likely to spread. A high Gleason Score means the cancer tissue is very different from normal and the tumor is more likely to spread (NCI Dictionary of Cancer Terms, 2024).

High Penetrance Breast Cancer Susceptibility Genes: Genes in which certain mutations are related to significantly increased likelihood of Breast Cancer. NCCN includes genes such as *BRCA1, BRCA2, CDH1, PALB2, PTEN, SKT11*, and *TP53* (NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic v1.2025).

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 (e.g., individual who is adopted) (NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic v1.2025).

Lynch Syndrome Associated Cancer: Colorectal, endometrial, gastric, Ovarian, pancreatic, urothelial, brain (usually glioblastoma), biliary tract, small intestinal cancers, sebaceous adenomas, sebaceous carcinomas and keratoacanthomas as seen in Muir-Torre syndrome (NCCN, Genetic/Familial High-Risk Assessment: Colorectal v2.2024).

Multi-Gene 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, 2024). For the purposes of this policy, a Multi-Gene Panel consists of five or more genes.

Ovarian Cancer: Includes fallopian tube cancers and primary peritoneal cancers as well as Ovarian Cancer (NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic v1.2025).

Penetrance: The probability of a clinical condition developing in the presence of a specific genetic variant/mutation (Daly et al., 2017).

Personal and Family History Documentation: In the form of a pedigree drawing/diagram utilizing 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, and Pancreatic v1.2025).

$PREMM_5$: PREdiction Model for gene Mutations. The $PREMM_5$ model estimates the overall cumulative probability of having an *MLH1, MSH2, MSH6, PMS2*, and *EPCAM* gene mutation. Mutations in these genes are related to Lynch syndrome (Kastrinos, 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 which are the same kind of cancer as the primary tumor (NCI Dictionary of Cancer Terms, 2024).

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) (NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic v1.2025).

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.

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)

CPT Code	Description
Multi-Gene 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)
0131U	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (13 genes) (List separately in addition to code for primary procedure)
0132U	Hereditary ovarian cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (17 genes) (List separately in addition to code for primary procedure)
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)
0135U	Hereditary gynecological cancer (e.g., hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (12 genes) (List separately in addition to code for primary procedure)
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
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

CPT Code	Description
Multi-Gene Panel	
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

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 5-10% of all cancers are hereditary (Heald et al., 2016). Hereditary cancers typically have an earlier age of onset and have an autosomal dominant pattern of inheritance observable in a family (NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic v1.2025).

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 of 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 exam performed by a clinician with familiarity with hereditary cancer syndromes. When applicable, risk assessment tools should be utilized 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, and Pancreatic v1.2025). Genetic testing is generally recommended when there is a personal or family history consistent with a hereditary cancer susceptibility, the test can be adequately interpreted, and 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 (NCI, 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 of 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, estimated risk is 60%-72% for women who are carriers of a pathogenic/likely pathogenic (P/LP) *BRCA1* variant and 55%-69% for *BRCA2* P/LP variant carriers. For Ovarian Cancer, cumulative risk (by age 70) associated with *BRCA1* P/LP variants is approximately 48.3% and for *BRCA2*, associated cumulative risk is approximately 20%. Breast and Ovarian Cancer are most notable, but 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, and/or pancreatic Cancer as well. (NCI, 2024; NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic v1.2025).

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, and Pancreatic v1.2025, NCCN, Genetic/Familial High-Risk Assessment: Colorectal v2.2024, NCCN, Prostate Cancer v4.2024).

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*, and *HOXB13*

Many Multi-Gene 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 within a single gene and across multiple genes. It is also possible that these Multi-Gene tests can, in the case of families where 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, and Pancreatic v1.2025; NCCN, Genetic/Familial High-Risk Assessment: Colorectal v2.2024; 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

Testing for *BRCA1* and *BRCA*2 mutations can include targeted analysis for pathogenic founder variants for 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 about 66% of *BRCA1/BRCA2*-associated hereditary breast and ovarian cancer syndrome (HBOC). Sequence analysis can identify variants in approximately 87-89% of cases for *BRCA1* and 97-98% of cases for *BRCA2*. Gene-targeted duplication/deletion testing identifies variants in eleven to thirteen percent of cases for *BRCA1* and two to three percent for *BRCA2* (Petrucelli et al., 2023). The risk of developing breast and ovarian cancer are significantly increased in individuals who inherit a harmful variation in *BRCA1* or *BRCA2*; over 60% of women with these variants with 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 cancer in the contralateral breast in the future. Approximately 39%-58% of women with a harmful mutation in *BRCA1* and 13%-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 to only 1.1% of women in the general population. There is also evidence that variations in *BRCA1* or *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 [NCI], 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 patients with triple-negative disease, *BRCA* mutation carriers were diagnosed at a younger age compared with non-carriers (NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic v1.2025). 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 of 51 years), Gonzalez-Angulo et al. (2011) found a 19.5% incidence of *BRCA* mutations. The authors recommend that genetic testing be discussed with all patients 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 4267 individuals from the US, Italy, and Poland. The length of the research period for the studies varied from a minimum of two years to a maximum of 36 years, with average duration of 14 years. Based on their analysis, the reviewers assert that *BRCA1/2* testing benefits first-degree relatives of individuals with FPC, who have two to ten times higher risk than the general population of developing FPC. Identifying *BRCA1/2* mutations is important not only for FPC risk, but also broader cancer risks such as HBOC. *BRCA1/2* testing has also shown to be beneficial for 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 correlate with improved overall survival (OS) when compared to mutation-free pancreatic cancer due to targeted treatment options (Toss et al., 2019; Puccini et al., 2022). The authors recommend *BRCA1/2* testing for diagnostic and prognostic purposes for first -degree relatives of individuals diagnosed with FPC and encourage further study with large samples 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 that were referred for molecular testing due to suspicion of HBOC. Prevalence data was analyzed for individuals from different risk and ethnic groups. Subjects 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 not meeting 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 subjects considered high-risk was 23.8% vs 8.2% for the elective group. The mutation profile for individuals at high-risk was 90.1% sequencing mutations vs 9.9% LRs, and for elective patients was 94.1% sequencing vs 5.9% LRs. The authors noted that this difference may reflect the bias in subjects at high-risk to carry mutations in *BRCA1*, which has a higher penetrance and frequency of LRs compared with *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 breast cancer probands with a family history of pancreatic cancer, Stadler et al. (2012) found that 30 (14.2%) harbored a *BRCA* mutation. Fourteen (47%) of the mutations were in *BRCA1* and sixteen (53%) were in *BRCA2*. Subjects 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 subjects with a first-, second-, or third-degree relative with pancreatic cancer, mutation prevalence was 15.4%, 15.3% and 8.6%, respectively. The authors found that *BRCA1* and *BRCA2* mutations are 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 subjects with resected *BRCA* mutation-associated pancreatic adenocarcinoma (PAC) to 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 subjects (two with *BRCA1* [1.3%] and six with *BRCA2* [4.1%]). A previous cancer was reported by 24% (35/145) of subjects, with the most 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, and Pancreatic Cancer Multi-Gene Panels

In a recent cohort study, Whitworth et al. (2022) sought to answer this 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 of individuals with breast cancer on clinical decision-making. The study included 952 individuals between the ages of 18 and 90 years with a diagnosis of breast cancer who had not previously undergone either single or multigene testing. Individuals 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 individuals with breast cancer were made available. For individuals found to have a P/LP variant, changes in recommended management were reported for 83.8% (31/37) of in-criteria individuals and 67.6% (23/34) of out-of-criteria individuals. Testing results led to a change in recommendations for 63.6% (14/22) of out-of-criteria individuals with a variant in a breast cancer predisposition gene. Multigene testing was considered helpful for two-thirds of individuals with P/LP variants, and for one-third of the individuals with results that were either negative or found variants of uncertain significance (VUS). No changes were made for 98.9% of participants with negative results or VUS. 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, several limitations were noted, including the lack of documentation of cancer stage at diagnosis; study sites were primarily breast surgery practices so individuals 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 individuals for PARP inhibitor treatment eligibility. The out-of-

criteria population is skewed to individuals older than 45 (per NCCN guideline requirements) and there was no ongoing follow up for determination of longer-term outcomes. Lastly, the study was sponsored by a multigene test manufacturer and several of the authors had affiliations with the sponsor, creating 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 woman 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 suggests 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.

Alvarado et al. (2020) evaluated 3162 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. 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. Breaking the subset down to only those with 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. Eighty-five women were tested with a multigene panel and of those, 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 (ClinGen) 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 2 genes had a Moderate classification. In the Limited group, 6 of 31 for breast cancer and 6 of 32 for ovarian cancer were defined. Inconsistent evidence resulted in Disputed or Refuted assertions for 9/31 genes for breast and 4/32 genes for ovarian cancer. No Reported Evidence of disease association was found for 5/31 genes for breast and 11/32 for ovarian cancer. The study demonstrated that there is still some development to be done prior to having standardized panels.

Shimelis et al. (2018) aimed to define the cancer genes associated with an increased risk of triple-negative breast cancer (TNBC). A large cohort of subjects with TNBC was assembled and multi-gene panel testing of 21 genes in 8753 participants was performed by a clinical testing laboratory (Ambry Genetics, Alisa Viejo, CA). Additionally, testing of 17 genes in 2148 participants from a previous Triple-Negative Breast Cancer Consortium (TNBCC) study were included. The study found that germline pathogenic variants in *BARD1, BRCA1, BRCA2, PALB2,* and *RAD51D* were associated with high risk (odds ratio > 5.0) of TNBC and greater than 20% lifetime risk for overall breast cancer among Caucasians. Pathogenic variants in *BRIP1, RAD51C*, and *TP53* were associated with moderate risk (odds ratio > 2) of TNBC. Comparable trends were observed for the African American population. Pathogenic variants in these TNBC genes were detected in 12.0% (3.7% non-*BRCA1/2*) of all participants. The researchers concluded that multi-gene hereditary cancer panel testing can identify genes that give an elevated risk of TNBC.

Crawford et al. (2017) evaluated 300 women who had previously tested negative for pathogenic variants in *BRCA1/2* by either limited or comprehensive sequencing. All of the study subjects 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 nine percent of the total population of the study had pathogenic mutations associated with heritable cancer risk and eight percent 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 multi-gene panel testing which has important implications for family testing.

Clinical Practice Guidelines

American College of Medical Genetics and Genomics (ACMG)

In a 2020 statement, ACMG explored the evidence supporting *BRCA1/2* and other inherited breast cancer genetic testing for all individuals diagnosed with breast cancer (Pal et al., 2020). Although they recommend that all patients with breast cancer be evaluated regarding 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 individual diagnosed with breast cancer, especially in the case of multi-gene 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 individuals during genetic counseling with a trained genetics professional or a health care provider with expertise in cancer genetics, and any individual 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 or 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 VUS.

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 or several close relatives that 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 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.
  - 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 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 guideline (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 individual's history and/or test results are complex, referral to a certified genetic counselor or genetics professional may be helpful.
- Multi-gene panels are increasingly available for screening purposes. There is a lack of consensus among experts regarding which genes should be tested in different clinical scenarios.
- Genetic testing should be made available to all individuals with a personal history of breast cancer.
- Individuals who have had genetic testing previously may benefit from updated testing.
- Genetic testing should be made available to individuals without a history of breast cancer when NCCN guidelines are met. Unaffected individuals should be informed that testing an affected relative first, whenever possible, is more informative than undergoing testing themselves.
- VUS are not clinically actionable and are considered inconclusive. Individuals should be managed on their risk factors, and not a VUS result.

American Society of Clinical Oncology (ASCO)

ASCO published a guideline for genetic testing in women with a diagnosis of epithelial ovarian cancer (Konstantinopoulos, 2020). This was the result of a systematic review of 19 identified studies including randomized controlled trials (RCTs), 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 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 diagnosis and management of hereditary cancer should conduct the genetic evaluations, and first- or second-degree blood relatives of an individual with ovarian cancer and a known gene variant should be offered counseling, evaluation, and testing as well. VUS should not drive clinical decision making.

ASCO convened an expert panel to determine recommendations for male breast cancer management and recently published the results (Hassett et al., 2020). The panel used 26 studies as the basis of the recommendations. While the majority of recommendations concerned treatment options, the panel did recommend 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).

An ASCO policy statement update in 2015 (Robson et al.) recommended that genetic testing for cancer susceptibility be performed when the following three criteria are met: the individual being tested has a personal or family history suggestive of genetic cancer susceptibility, the test can be adequately interpreted, and the test results have accepted clinical utility.

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

In 2024, ASCO and SSO (Bedrosian et al.) published recommendations for germline mutation testing for individuals 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 results of the review and discussion, the following recommendations for germline genetic testing were made:

- Individuals 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%).
- Individuals 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 poly (ADP–ribose) polymerase (PARP) inhibitor therapy for early-stage or metastatic disease.
  - Have triple-negative breast cancer.
  - Have personal or family history suggesting the possibility of a pathogenic variant.
  - 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%).
- Individuals 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 individual 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%).
- Individuals with a second primary cancer, either in the contralateral or ipsilateral breast, should be offered *BRCA1/2* testing (Formal Consensus; Agreement: 89.74%).

- Individuals 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%).
- Individuals with a personal history of breast cancer diagnosed at age 66 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 pathogenic variant.
  - 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 risk of second primary cancer as well as informing 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, risk of second primary cancer or family risk assessment may be informed by such testing and may be offered to individuals undergoing *BRCA1/2* testing when appropriate (Formal Consensus; Agreement: 87.50%).
- An individual's personal and family history should be considered if a multigene panel is ordered (Formal Consensus; Agreement: 91.43%).
- VUS should not change management (Formal Consensus; Agreement: 88.57%).

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

European Society of Medical Oncology (ESMO)

ESMO's recent clinical practice guidelines for diagnosis, treatment, and follow-up of early breast cancer (Loibl et al., 2024) recommend germline testing and genetic counseling for individuals with pathogenic variants 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 individuals with significant family history (Grade of recommendation: A). Panels should be comprised of clinically validated HBOC genes (*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, PALB2, PTEN, RAD51C, RAD51D, STK11, TP53*). The authors point out that screening panels 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 and Pancreatic Cancer guidelines (v1.2025) present evidence-based criteria for genetic testing for hereditary breast, ovarian, and/or pancreatic cancer, noting that an individual's personal and/or family history can often be explained by more than just one inherited cancer syndrome. Multi-gene testing simultaneously evaluates genes for hereditary cancer types associated with a specific family phenotype (or multiple phenotypes). Phenotype-directed testing using tailored, multi-gene panel tests can be more efficient and cost-effective and increase potential for detection of P/LP variants in individuals at risk. For individuals who have tested negative for a single syndrome, but whose personal/family history suggests hereditary susceptibility, such testing may also prove 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; 3) low probability that testing will find documented high-penetrance genes.

Per NCCN guidelines, hereditary cancer testing is clinically indicated in the following general situations:
- An individual has any blood relative with a known P/LP variant in a cancer susceptibility gene.
- An individual has previously tested negative with limited testing (e.g., single gene or absent deletion duplication analysis), meets testing criteria below, and desires multi-gene 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.
- Individual meets Li-Fraumeni syndrome, Cowden syndrome/PTEN hamartoma tumor syndrome or LS testing criteria.

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

Breast Cancer

For individuals 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*, and *TP53*) is clinically indicated in the following situations (also see general testing criteria above):

- Individual has a personal history of breast cancer with the following features:
  - Diagnosed ≤ 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
      - 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 an individual assigned male at birth.
    - Individual is of Ashkenazi Jewish ancestry.
    - Individual has at least one close blood relative with:
      - Breast cancer at age 50 or younger.
      - Male breast cancer.
      - Ovarian, pancreatic, or metastatic, or high- or very-high risk group prostate cancer.
    - There are 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.
- Individual is unaffected or affected but does not meet criteria above and:
  - Has a first- or second-degree blood relative that meets any above criteria (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making).
  - Has a probability > 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:

- Individual has a personal history of breast cancer at age 65 or younger and does not meet any of the above criteria *Caution: The majority of those pathogenic variants (PVs) will be in moderate penetrance genes, which are over-represented in older affected individuals. Access to an experienced genetic counseling team to discuss management options is especially important in this setting.
- Individual 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.
- Individual is unaffected or affected but does not meet any of the above criteria and has a 2.5%–5% probability of *BRCA1/2* P/LP variant based on prior probability models (e.g., Tyrer-Cuzick, BRCAPro, CanRisk).
- Individual 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:

- Individual 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.
- Individual is diagnosed with localized prostate cancer with Gleason Score < 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 individuals 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*, and *RAD51D*) is clinically indicated in the following situations (also see general testing criteria above):

- Individual has a personal history of epithelial ovarian cancer (including fallopian tube or peritoneal cancer) diagnosed at any age.
- Individual unaffected with ovarian cancer has family history including one of the following:

- Individual has a first- or second-degree blood relative with epithelial ovarian cancer (including fallopian tube or peritoneal cancer) diagnosed at any age.
- Individual does not meet criteria above but has a probability > 5% of a *BRCA1/2* P/LP variant based on prior probability models (e.g., TyrerCuzick, BRCAPro, CanRisk).

Pancreatic Cancer

For individuals 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*, and *TP53*) is clinically indicated in the following situations (also see general testing criteria above):

- Individual has a personal history of exocrine or neuroendocrine pancreatic cancer.
- Individual has a first-degree relative diagnosed with exocrine pancreatic cancer.

Prostate Cancer

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

- Individual has a personal history of prostate cancer with the following features:
  - Tumor is:
    - Metastatic.
    - High- or very-high risk group.
  - Individual has ancestry/family history including:
    - At least one close blood relative with:
      - Breast cancer diagnosed age 50 or younger.
      - Triple negative breast cancer at any age.
      - Breast cancer in an individual assigned male at birth at any age.
      - Ovarian cancer at any age.
      - Pancreatic cancer at any age.
      - Metastatic 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.
- Individual is unaffected, or affected but does not meet above criteria, and has a first-degree blood relative meeting any of the criteria above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making).

Testing for prostate cancer susceptibility genes may be considered when an individual has a personal history of prostate cancer and intermediate-risk prostate cancer with intraductal/cribriform histology.

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. NSGC notes the complexities of genetic testing and stresses the importance of involving genetic counselors and other experts who are able to provide education regarding the appropriate utilization of such testing to avoid undo harm and/or unnecessary costs.

In 2021, the NSGC published a new practice resource which 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 for individuals 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 individuals with P/LP variants within less common, high-penetrance or moderate-penetrance genes and ongoing research is being done 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.
- Discussion of dissemination of information regarding testing performed and implications on testing of other family member.
- 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 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 for whom 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 Cancer Syndromes (Including Lynch Syndrome Associated Cancers)

In an effort to determine the yield and possible impact of multigene panel testing (MGPT) on clinical decision-making, Coughlin et al. (2022) conducted a retrospective cohort study including 34,244 individuals with a history of colorectal cancer (CRC). All participants underwent MGPT using panel tests containing at least ten genes. The participants were largely female (60.7%), White (70.6%) and 50 years of age or older (68.9%). A total of 4864 individuals (14.2%) were found to have one or more P/LP germline variants and 3111 (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 of larger gene panels with a higher yield of clinically actionable P/LP variants. P/LP variants were more common in those with Hispanic ethnicity ($p < .001$) and in individuals of Ashkenazi Jewish descent ($p < .001$). The overall rate of clinically actionable P/LP variants found on MGPT across all panel sizes, races, and ages was at least 7.9%. VUS were identified in 13,094 individuals (38.2%). Based on these results, the authors concluded that MGPT of individuals with CRC identified high rates of clinically actionable variants across individuals of 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 individuals with CRC, even if CRC was not the primary reason for the individual 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 multi-gene panel testing 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, multi-site design and a > 80 gene NGS platform to perform testing on individuals with CRC. A total of 361 adults participated (median age of 57 years). Pathogenetic germline variants were found in 15.5% (n = 56) of participants in the study and 9.4% (n = 34) had clinically actional findings that would not have been detected with a CRC specific gene panel or if standard clinical practice criteria had been followed. Overall, 11% (1 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 was the demographic of the participants seen at the Mayo Clinic sites where the study was conducted, which may limit 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 that 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 multi-gene cancer panels for hereditary CRC syndromes. For polyposis syndromes that include familial adenomatous polyposis (FAP), attenuated FAP (AFAP), MUTYH-associated polyposis (MAP), 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, there are many genes that 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 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 or EC. The panel recommends universal screening of all patients with CRC or EC at any age with tumor showing evidence of mismatch repair deficiency (dMMR), either by microsatellite instability (MSI) or loss of mismatch repair (MMR) protein expression.
Using the ClinGen 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, 14/42 (33.3%) were Definitive, 1/42 (2.4%) was Strong, 6/42 (14.3%) were Moderate, 18/42 (42.9%) were Limited, and 3/42 (7.1%) were either No Reported Evidence, Disputed, or Refuted. The researchers state 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 individuals with hereditary gastrointestinal cancer syndromes, including genetic testing recommendations (Syngal et al., 2015). The authors note that genetic testing is widely available and should be standard of care for individuals at increased risk for a hereditary cancer syndrome. The guidelines recommend targeted gene analysis for the syndrome most likely to be responsible for an individual's symptoms. The authors address multi-gene panels and NGS technology, noting that genetic specialists are increasingly using NGS panels for individuals 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 when compared to sequentially screening the possible list of genes. It is additionally noted, however, that even though there might be efficiency compared to sequential screening, the time to results is typically longer for large panels. The larger the panel, the more likely it is that VUS will be found. In addition, the authors caution that these panels often include genes for which there is 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 do not recommend multiple gene sequencing but note 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)

For hereditary cancer syndromes associated with CRC and polyposis, MGPT has been accepted, however the genes included on commercially available panels vary widely. The CGA-IGC performed an evidence review to determine which genes should be included on a multigene panel for an individual with a suspected hereditary CRC or polyposis syndrome (Heald et al., 2020). In addition, the group proposed updated genetic testing criteria. The collaborative group highlighted the following genes associated with LS: *MLH1, MSH2, MSH6, PMS2, EPCAM* and the genes associated with polyposis syndromes: *APC, BMPRIA, MUTYH, PTEN*, *SMAD4*, and *STK11*. These genes were noted as the minimum genes that should be included on a multigene panel for these conditions. The CGA-IGC recommends multigene panel for individuals with the following:

- CRC diagnosed at before 50 years of age.
- Multiple LS primary tumors.
- CRC and at least one first degree relative with CRC or EC.
- $PREMM_5$ score ≥ 2.5% or MMRpro or MMRpredict score ≥ 5%.
- dMMR CRC, not attributed to MLH1 promoter methylation.
- Individuals meeting any other genetic testing criteria.
- ≥ 10 cumulative colorectal adenomas.
- ≥ 3 cumulative gastrointestinal hamartomatous polyps.

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 individuals have been identified to have germline heterozygous P/LP variants in the MMR genes including *MLH1, MSH2, MSH6* or *PMS2* or 3' terminal deletions of *EPCAM*. The following clinical criteria are provided for identifying individuals who should be evaluated for LS:

- Individual has a family history of a known germline MMR pathogenic/likely pathogenic variant.
- Individual has a personal history of CRC or EC with any of the following characteristics:
  - Age of diagnosis less than 50 years.
  - Tumor is dMMR: MSI-high or abnormal MMR immunohistochemistry (IHC).
  - Another LS-related cancer*.
  - Family history of LS-related cancers in first or second-degree relatives.

    - ≥ 1 relative(s) diagnosed at age < 50 years.
    - ≥ 2 relatives diagnosed at any age.
- Family history of cancer meeting any of the following criteria:
    - ≥ 1 first-degree relative(s) with CRC or EC diagnosed age < 50 years.
    - ≥ 1 first-degree relative(s) with > 1 diagnoses of LS-related cancers.
    - ≥ 2 or more first-or second-degree relatives with LS-related cancers with ≥ 1 diagnosed age < 50 years.
    - ≥ 3 or more relatives with LS-related cancers at any age.
- Genetic risk model score ≥ 5% predicted probability of germline MMR pathogenic/likely pathogenic variant (e.g., PREMM$_5$, MMRpro).

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

NCCN

The NCCN guidelines present evidence-based criteria for genetic testing of individuals who may have hereditary high-risk CRC/EC syndromes (NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric v2.2024). 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 individuals with CRC or EC for testing, because they have greater sensitivity for identifying individuals affected with LS and other cancer risk genes than selecting specific germline testing based on family history or tumor-based criteria. When used, germline 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, POLD1, POLE,* and *BRCA1/2.* Use of panels including 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 multi-gene tests may differ substantially on the specific genes analyzed by the panel, the total number of genes analyzed, and turn-around time, among other things. NCCN advises that the choice of specific laboratory/test panel is critical and that multigene testing is ideally offered with professional genetic expertise in cancer genetics, including pre- and post-test counseling.

Lynch Syndrome (LS) 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.
- Individual 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.
- Individual has a family history of any of the following:
    - One or more first-degree relatives with a CRC or EC diagnosed at 49 years of age or younger.
    - One or more first-degree relatives with a 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 or younger.
    - Three or more first-or second-degree relatives with LS-related cancers at any age.
- Individual has a five or greater percent risk of MMR gene pathogenic variant based on predictive models (PREMM$_5$, MMRpro, MMRpredict).
    - Individuals with personal history of CRC and/or EC with a PREMM$_5$ score of 2.5% or greater should be considered for MGPT.
    - Individuals with no personal history of CRC and/or EC may use a PREMM$_5$ score of ≥ 2.5% rather than ≥ 5% to select individuals for MMR testing, when used with clinical judgement.
- Personal history of a tumor with dMMR determined by PCR, NGS, or IHC, 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 maybe be considered for individuals with a personal history of CRC or EC at 50 years of age or older and untested for dMMR status in a tumor or a documented absence of dMMR in tumor.

Adenomatous Polyposis Testing Criteria

Testing is recommended when:

- Individual has a personal history of twenty or more cumulative adenomas.
- Family history of a known pathogenic variant in an adenomatous polyposis genes.
- Individual has multifocal/bilateral congenital hypertrophy of retinal pigment epithelium (CHRPE).
- Individual 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:

- Individual has a personal history of a desmoid tumor, hepatoblastoma, unilateral CHRPE.
- Individual meets criteria for serrated polyposis syndrome (SPS) and has at least some adenomas.
- Individual has a personal history of between 10 and 19 cumulative adenomas.

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

- Individuals meeting one or more of the other adenomatous testing criterion above after reevaluation of personal and family history.
- Individuals diagnosed with any cancer at less than 30 years of age.

Age of 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 (AGA), American College of Gastroenterology (ACG), and American Society for Gastrointestinal Endoscopy (ASGE), and at times including other experts when needed for additional expertise. In 2022, this group published recommendations for diagnosis and management of cancer risk in the gastrointestinal hamartomatous polyposis syndromes (Boland, et al., 2022), including the following regarding genetic evaluation and testing:

- Individuals 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 a MGPT. (Strong recommendation, low quality of evidence).
- Genetic evaluation should be performed for any individual with the following: 1) two or more histologically confirmed Peutz-Jeghers polyps, 2) any number of Peutz-Jeghers polyps in an individual who has a family history of Peutz-Jeghers syndrome in a first-degree relative, 3) characteristic mucocutaneous pigmentation in a person with a family history of Peutz-Jeghers syndrome, 4) any number of Peutz-Jeghers polyps in a person with the characteristic mucocutaneous pigmentation of Peutz-Jeghers syndrome. (Strong recommendation, low quality of evidence).
- Genetic evaluation for any individual 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, (3) any number of juvenile polyps and one or more first-degree relative with juvenile polyposis syndrome is recommended. (Strong recommendation, low quality of evidence).
- The task force suggests that individuals with *SMAD4* pathogenic variants 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).
- Individuals with multiple gastrointestinal hamartomas or ganglioneuromas should undergo genetic evaluation for Cowden's syndrome and related conditions. (Strong recommendation, low quality of evidence).

Other Cancers or More Than One Hereditary Cancer Syndrome

In an effort 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 CDC Tier One heritable conditions (HBOC, LS, and familial hypercholesterolemia), as well as evaluating downstream clinical impact. Samadder and colleagues focused on subjects that had undergone Exome+ sequencing (Helix Inc., San Mateo, CA) for specific results suggesting HBOC (*BRCA1/2*) and LS (*MLH1, MSH2, MSH6, PMS2* and *EPCAM*), performing a corresponding chart review to compile demographics along with 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*, and 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 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 = .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 of individuals affected with HBOC and LS cancer predisposition syndromes. Study results indicate that screening via Exome+ could potentially detect approximately 50% of CDC Tier One condition carriers who would otherwise not be identified based on current processes. Several limitations, however, were identified, including 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 (SNVs) and small indels, which led to some false negative results due to lack of detection of copy number variants that are estimated to be pathogenic in 5-25% 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 evaluating best approaches for population-based genetic screening is needed before such screening can be adopted as standard practice.

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 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 individuals 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 individuals. Existing practice guidelines recommend sequential gene testing strategies determined by individual clinical features; however, the authors indicate that these guidelines were developed prior to the routine availability and use of MGPT. A total of 1727 individuals who received targeted MGPT related to suspicion of hereditary PPGL were included in the review. The analysis revealed that 27.5% of the individuals 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%). Individuals with extra-adrenal location of disease, early age of onset, 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* only would miss approximately 1/3 (32.8%) of individuals with PVs. Overall, the researchers concluded that the data from this study indicate high diagnostic yield in individuals with and without known risk factors, significant contribution to diagnostic yield from rare genes, and a low rate of inconclusive results which supports the use of universal testing with MGPT for all individuals with PPGL, regardless of tumor type, age of onset, metastatic disease, syndromic features, family history, or functional status.

Nölting et al. (2022) published a review integrating current guidelines and expert opinions regarding the personalized management of pheochromocytoma and paraganglioma (PPGLs). PPGLs have the highest rate of heritability among all tumors with approximately 30% of 35% of Caucasian individuals (lesser percentage in Chinese population) showing germline mutations. In addition, 35% to 40% of Caucasians (higher in the Chinese population) have 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 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 which used an NGS panel with greater than 80 genes to perform germline sequencing on 250 individuals with pancreatic cancer. Included individuals were not selected for 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. VUS were found in 44.4% of participants. Individuals with a family history of cancer were associated with a higher risk of PGV. 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 individuals with pancreatic cancer were carriers of PGV. The authors recommend 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 individuals with cancer through the use of a universal approach rather than targeted testing based on clinical practice guidelines. A total of 2984 individuals 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 to the standard guideline-directed approach and also assess the uptake of cascade family variant testing. PGVs were detected in 397 participants (13.3%), and 1415 participants (47.4%) were found to have 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 for 42 study subjects. A younger age of diagnosis (mean age was 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 FVT. The authors concluded that the universal MGPT of individuals 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 being free to family members, uptake of cascade FVT 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 need for testing used by the expert reviewers for the study underwent a change during the course of the study which may have impacted outcome. Lastly the demographics of 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 in order to study the effect of MGPT for hereditary cancers. The cohort consisted of 165,000 patients 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 that met the testing criteria for only *BRCA1/2* (33.1%) or only LS (46.2%). For individuals that 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 pheochromocytoma and paraganglioma (PPGL), 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 management of these conditions for afflicted individuals and their family members. The authors indicate 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 (SDHx), *TMEM127* or *MAX*. They state at a minimum, testing for *FH, NF1, RET, SDHB, SDHD* and *VHL* for individuals with PPGL should be done, but also recommend *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 to using multi-gene 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 SDHx genes, *MAX, 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 notes that up to 35% of PPGLs are hereditary and diagnosis is based on molecular genetic testing which should be offered to any affected individual.

An analysis of 252,223 individuals (most of whom were suspected to have HBOC or LS) was performed by Rosenthal et al. (2017) through the use of a 25-gene pan-cancer panel. Of these individuals, the majority (92.8%) met testing criteria for HBOC and/or LS. PVs were identified in 6.7% of the tested individuals, 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 individuals who met only HBOC criteria were in non-*BRCA1/2* genes. Likewise, in individuals who met LS criteria, half of the pathogenic variants identified were in non-LS genes. These researchers suggest 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 (EAPPR) has released data showing that 80% of individuals in their registry had a germline mutation, compared to previous smaller pediatric case series which estimated a germline mutation prevalence of 30-40%. 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 participants, 44 (80%) had a germline mutation with the majority found to have either *VHL* (38%) or *SDHB* (25%) mutation. The authors concluded that the majority of pediatric patients with PPGL likely have detectable germline mutations and thus, 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 individuals diagnosed with kidney cancer. Participants were tested at a commercial laboratory from August 2013 to June 2016. Clinical characteristics such as age, gender, age of diagnosis, ordering institution, kidney cancer histology, personal history, and cancer history were obtained from test requisitions. In total, 1235 participants with renal cell carcinoma had testing. The majority of the cohort was Caucasian (64%) and male (54%). The average age of diagnosis was 46. Histology was available on 942 participants and common tumor histology such as clear cell, papillary and chromophobe kidney tumors was present in 67% of these. 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 for cancer was reported in 1007 participants, and of these, 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%, non-oncology physicians referred 1%, and other healthcare 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 note 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 VUS 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 VUS where it may not be warranted. However, this is the first publication to report on the results for a large cohort for kidney cancer patients undergoing multi-gene 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 individuals 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 and were published as an ASCO guideline (Tung et al., 2024). Recommendations are summarized as follows:

- All individuals 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 individuals diagnosed with cancer if there is more than one relevant gene (Evidence Quality: Not rated; Strength of recommendation: Strong).
  - The panel should, at a minimum, include at least the more strongly recommended genes for the individual based on 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 by 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 individuals 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 including these genes for any individual 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*

Cancer Type	More Strongly Recommended	Less Strongly Recommended
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*
Phaeochromocytomas and paragangliomas	*FH, MAX, RET, SDHA, SDHB, SDHC, SDHD, TMEM127, NF1, VHL*	*EGLN1, EPAS1, KIF1B, MET, SDHAF2*
Prostate cancer	*BRCA1, BRCA2, EPCAM, HOXB13, MLH1, MSH2, MSH6, PMS2*	*ATM, CHEK2, PALB2*
Renal cell carcinoma	*BAP1, FH, FLCN, MET, SDHA, SDHAF2, SDHB, SDHC, SDHD, PTEN, VHL*	*TSC1, TSC2*
Sarcoma	*TP53*	*NF1, RB1*

- When an individual meets criteria for germline testing, it should be offered regardless of results from tumor testing (Evidence Quality: Low; Strength of Recommendation: Strong).
- When tumor testing reveals a pathogenic variant in *BRCA1, BRCA2, BRIP1, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, RAD51C, RAD51D, RET, SDHAF2, SDHB, SDHC, SDHD, TMEM127, TSC2, VHL* and, only if patient < 30 years of age, *APC, PTEN, RB1*, and *TP53*, germline genetic testing should be offered regardless of germline genetic testing criteria. When tumor testing indicates a pathogenic variant in *ATM, BAP1, BARD1, CHEK2, DICER1, FH, FLCN, NF1, POLD1, POLE, SDHA* and, only if patient < 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 individuals with the gene/relevant tumor types in the below table (Evidence Quality: Moderate; Strength of Recommendation: Strong).

Gene	Relevant Tumor Types
ATM	Breast cancer, gastric cancer, epithelial ovarian cancer, pancreatic adenocarcinoma, or 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

Gene	Relevant Tumor Types
DICER1	DICER1 Pleuropulmonary blastoma, cystic nephroma, embryonal rhabdomyosarcoma, ovarian Sertoli-Leydig cell tumors, ovarian sarcoma, neuroblastoma, thyroid cancer
FH	Paraganglioma, pheochromocytoma, or renal cell carcinoma
FLCN	Renal cell carcinoma
NF1	Breast cancer, gastrointestinal stromal tumor (GIST), paraganglioma, pheochromocytoma
POLD1	Colorectal cancer
POLE	Colorectal cancer
SDHA	GIST, 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 pathogenic variants 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 with 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. There were several sections regarding genetic testing in Research Question 2 "Which individuals should undergo genetic testing for predisposition to pancreatic cancer?"; the provisional clinical opinion indicates that all patients with pancreatic adenocarcinoma 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 family history of cancer. The opinion also stated that germline genetic testing for cancer susceptibility should be considered in those with pancreatic cancer and unremarkable family history.

Genetic testing for cancer susceptibility may be efficient in circumstances where 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 VUS, it is recommended that providers with particular expertise in cancer risk assessment should be involved in the ordering and interpretation of MGPTs; especially those that include genes of uncertain clinical utility and genes not suggested by the patient's personal and/or family history (Robson et al., 2015).

NCCN

Prostate Cancer

NCCN Practice Guidelines for Prostate Cancer (v4.2024) direct the user to the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic and the NCCN Guidelines for Genetic/Familial High Risk Assessment: Colorectal, Endometrial and Gastric, and indicate that the criteria in those guideline should be referenced at the time of initial diagnosis of prostate cancer, and if applicable, at recurrence. Germline testing should be considered for appropriate candidates where the information obtained could impact prostate cancer treatment and/or clinical trial options, management of risk for other cancers, and potential risk in family members. If criteria in the above referenced guidelines are met, germline multigene testing should include at least *BRCA1, BRCA2, ATM, PALB2, CHEK2, HOXB13, MLH1, MSH2, MSH6*, and *PMS2*. In addition, individuals with prostate cancer undergoing tumor molecular analysis should be counseled that tumor testing using DNA sequencing may reveal germline findings as well.

Pancreatic Adenocarcinoma

NCCN Clinical Practice Guidelines for Pancreatic Adenocarcinoma (v3.2024) recommend germline genetic testing using comprehensive gene panels for hereditary cancer for any individual with confirmed pancreatic cancer and also those for 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, and Pancreatic and the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial and Gastric (for pancreatic cancer in LS). Genetic counseling is recommended for individuals with pancreatic cancer who test positive for a pathogenic mutation (*ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, PALB2, PMS2, STK11*, *TP53*) or have a positive family history of cancer, especially pancreatic cancer, regardless of mutation status.

Neuroendocrine and Adrenal Tumors

NCCN Clinical Practice Guidelines for Neuroendocrine and Adrenal Tumors (v2.2024) address genetic counseling and testing for individuals with neuroendocrine tumors (NETs), noting that the introduction of multigene genetic testing for hereditary endocrine neoplasias has quickly changed the clinical approach to genetic testing in these individuals. 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, PMS2*), multiple endocrine neoplasia (*MEN1*) and familial adenomatous polyposis (*APC*). The interpretation of genetic testing in these conditions, however, can be complex and subjective. Per the v2.2024 guideline, genetic risk evaluation and testing for hereditary endocrine neoplasia syndromes is recommended for individuals who meet any of the following criteria:

- Individual has adrenocortical carcinoma.
- Individual has pheochromocytomas or paragangliomas.
- Individual 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 for MEN2 due to medullary thyroid carcinoma or other combination of MEN2-related characteristics.
- A mutation was identified on tumor genomic testing that has clinical implications if identified in the germline.
- A close blood relative as 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.
- 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).

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

- Individual has gastrinoma (duodenal/pancreatic or type two gNET).
- Individual has multifocal PanNETs.
- Individual has duodenal/pancreatic NET at any age.
- There are other combinations of tumors or cancers in the patient and/or their family members.

Polygenic Risk Scores (PRS)

A 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 also with variants that have no known association with genes pertinent to a particular condition or disease (NCI Dictionary of Genetics Terms (2024). There is currently insufficient evidence to support the use of PRS for assessing hereditary cancer risk.

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 risk of early prostate cancer death in men with higher vs. lower genetic risk. A combination of modifiable lifestyle behaviors and genetic risk were used to categorize study participants, with a polygenic risk score (PRS) above median or a family history of cancer defining participants at higher genetic risk. Participants not meeting this 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 for MDCS and 65.1 years for HPFS. A total of 107 deaths by age 75 and 337 deaths after age 75 occurred due to prostate cancer. Those participants with higher genetic risk, as assessed by a PRS which included 400 genetic risk variants and/or family history including at least one first-degree relative with any cancer or prostate/breast cancer, had increased rates of both early and late prostate cancer death (HR, 3.26; 95% CI, 1.82-5.84, HR; 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 higher genetic risk made up 88% (94/107); 36% of those men (95% CI 12%-60%) were projected to be preventable through the performance of behaviors such as maintaining healthy weight, not 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 prostate cancer prevention tactics. Noted limitations include 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 study that better defines 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/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 J(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 interpret these findings to indicate that PRS accuracy is comparable to prostate specific antigen (PSA) testing or family history and note that the optimal method for calculating PRS is unclear at this time.

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 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 non-genetic 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 non-genetic risk factors had better discriminatory accuracy (AUC from 0.52 to 0.77) than those models that used PRS alone (AUC from 0.48 to 0.68), irrespective of the number of SNPs in the PRS. Based on these results, the authors concluded that breast cancer risk prediction models combining PRS with genetic and non-genetic risk factors appeared to be the most accurate, but additional study is required to better understand how these tools may be refined and applied in clinical practice.

American College of Medical Genetics (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 for clinical utility at this time. The document points out that a low PRS does not rule out significant risk of the disease/condition in question and could have poor predictive value if the individual considered for testing is of 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 individuals considering PRS have a discussion with their provider or counselor for discussion of test limitations and information regarding how PRS results may guide clinical management. Such management should be consistent with 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 individual 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 Multi-Gene 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 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 of Ambry Genetics with 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 on 1000 individuals with suspected hereditary cancer syndromes. The RNA testing coupled with DNA testing was performed and the RNA testing identified seven subjects 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 is performed, although the study did not clarify what proportion of variants received new classification or confirmation from RNA testing and what proportion were 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 after DNA testing to determine if RNA testing improved the data. The study included individuals and/or families with HBOC, LS, and hereditary diffuse gastric cancer. Only 93 of 909 eligible families sent in additional tests. The RNA testing results clarified the interpretation of 49 of 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 that had undergone only DNA testing; the researchers determined that 7265 of these had inconclusive variants that affect splicing. The authors concluded that approximately 1 in 43 individuals could potentially benefit from RNA testing if performed in every individual undergoing genetic assessment for hereditary cancer. The researchers call out several limitations, including participant availability to submit additional blood samples for RNA genetic testing and limited medical management data due to the number of surveys completed. Studies which include clinical impact of concurrent RNA/DNA genetic testing are needed to provide a full assessment of potential impact of RNA panel testing.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Laboratories that perform genetic tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) Act of 1988. More information is available at: https://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124105.htm. (Accessed November 1, 2024)

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 November 1, 2024)

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Policy History/Revision Information

Date	Summary of Changes
04/01/2025	**Coverage Rationale** • Replaced references to "Primary Solid Tumor *Cancer(s)*" with Primary Solid Tumor(s)" ***Individuals With a Personal History of a Primary Solid Tumor*** • Added language to indicate *BRCA1/2* gene testing is proven and medically necessary for individuals with a personal history of Breast Cancer diagnosed at age 65 or younger • Replaced language indicating "genetic testing with a Multi-Gene hereditary cancer Panel *or testing of BRCA1/2* for individuals with a personal history of a Primary Solid Tumor *cancer* (excluding basal or squamous cell skin cancer) is proven and medically necessary when at least one of the [listed] criteria are met" with "genetic testing with a Multi-Gene 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 [listed] criteria are met" • Revised coverage criteria for genetic testing with a Multi-Gene hereditary cancer panel for individuals with a personal history of a Primary Solid Tumor (excluding basal or squamous cell skin cancer): ○ Added criterion requiring the "individual has a personal history of malignant phyllodes tumors" ○ Replaced criterion requiring: ▪ "Individual has a personal history of Breast Cancer and individual *is a cisgender, transgender, or gender diverse individual* assigned male at birth" with "individual has a personal history of Breast Cancer and individual *was* assigned male at birth" ▪ "Individual has a personal history of Breast Cancer and at least one first- or second-degree relative with a BRCA-Related Cancer" with "individual has a personal history of Breast Cancer *or Prostate Cancer* and at least one first- or second-degree relative with a BRCA-Related Cancer" ▪ "Individual has a personal history of Ovarian Cancer, fallopian tube cancer, and/or primary peritoneal cancer" with "individual has a personal history of Ovarian Cancer *(including* fallopian tube cancer and/or primary peritoneal cancer)" ▪ "Individual has a personal history of paraganglioma or pheochromocytoma" with "individual has a personal history of *neuroendocrine tumor (e.g., adrenocortical carcinoma,* paraganglioma, or pheochromocytoma" ▪ "Individual has a personal history of a Primary Solid Tumor and a *BRCA1/2* pathogenic variant was detected in tumor tissue" with "individual has a personal history of a Primary Solid Tumor and 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, and TP53)*" ***Individuals With No Personal History of a Primary Solid Tumor*** • Revised coverage criteria for genetic testing with a Multi-Gene 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): ○ Added criterion requiring the individual has: ▪ At least one first- or second-degree relative with a history of Triple-Negative Breast Cancer ▪ At least one first- or second-degree relative with a history of Breast Cancer and relative was assigned male at birth ○ Replaced criterion requiring the: ▪ "Individual has at least one first-degree relative with a history of paraganglioma or pheochromocytoma" with "individual has at least one first-degree relative with a history of *neuroendocrine tumor (e.g., adrenocortical carcinoma,* paraganglioma, or pheochromocytoma" ▪ "Individual has at least one first- or second-degree relative with a history of Ovarian Cancer, fallopian tube cancer, and/or primary peritoneal cancer" with "individual has at

Date	Summary of Changes

	least one first- or second-degree relative with a history of Ovarian Cancer *(including* fallopian tube cancer and/or primary peritoneal cancer)"
	Unproven/Not Medically Necessary
	• Added language to indicate genetic testing for the purpose of polygenic risk scoring for hereditary cancers is unproven and not medically necessary for all indications
	Definitions
	• Updated definition of:
	  ○ High Penetrance Breast Cancer Susceptibility Genes
	  ○ Limited Family History
	Applicable Codes
	• Added CPT code 0495U
	Supporting Information
	• Updated *Description of Services*, *Clinical Evidence*, *FDA*, and *References* sections to reflect the most current information
	• Archived previous policy version 2025T0009PP

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, please 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).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.