

Genetic Testing for Hereditary Cancer (for Kentucky Only)

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[U Instructions for Use](#)

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Related Policies
None

Application

This Medical Policy only applies to the state of Kentucky.

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 Cancer

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 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 is a cisgender, transgender, or gender-diverse individual assigned male at birth
 - Breast Cancer and unknown or Limited Family History
 - Breast Cancer and at least one first- or second-degree relative with a [BRCA-Related Cancer](#)
 - Ovarian Cancer, fallopian tube cancer, and/or primary peritoneal cancer
 - Pancreatic cancer
 - Metastatic prostate cancer
 - [Cancer Associated with Lynch Syndrome](#)

- Paraganglioma or pheochromocytoma
- At least two different Primary Solid Tumor cancers (excluding basal or squamous cell skin cancer)
- Individual has a personal history of a Primary Solid Tumor cancer (excluding basal or squamous cell skin cancer) and a family history of cancer which includes at least one of the following:
 - At least one Close Blood Relative with a history of a [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 cancer (excluding basal or squamous cell skin cancer)
- Individual has a personal history of a Primary Solid Tumor cancer (excluding basal or squamous cell skin cancer) and at least one of the following:
 - A *BRCA1/2* pathogenic variant was detected in tumor tissue
 - Tumor tissue testing demonstrated that the cancer was MSI-high or had immunohistochemical staining showing the absence of one or more mismatch repair 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 PREMM5, 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 Cancer

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](#) cancer (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 Tumor cancers (excluding basal or squamous cell skin cancer)
 - [Cancer Associated with Lynch Syndrome](#)
 - Paraganglioma or pheochromocytoma
- 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
 - Metastatic prostate cancer
 - Ovarian Cancer, fallopian tube cancer and/or primary peritoneal cancer
 - Pancreatic cancer
- 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
- 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 cancer (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
- A personal history of colorectal polyposis with at least ten adenomas
- Any of the following:
 - Individual has a Tyrer-Cuzick, BRCAPro, or Penn11 Score of 5% or greater for a *BRCA1/2* pathogenic variant
 - Individual has a PREMM5, 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.

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 v1.2024).

Breast Cancer: Either invasive carcinomas or non-invasive (in situ) ductal carcinoma types (NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic v1.2024).

Close Blood Relatives: Are defined as follows (NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic v1.2024):

- 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: 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, 2023; NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic v1.2024).

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, 2023).

High Penetrance Breast Cancer Susceptibility Genes: Genes in which certain mutations are related to significantly increased likelihood of Breast Cancer. NCCN includes BRCA1, BRCA2, CDH1, PALB2, PTEN, SKT11, and TP53 (NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic v1.2024).

Limited Family History: Defined as having 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 v1.2024).

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 v1.2024).

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, 2023). 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 v1.2024).

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 v1.2024).

PREMM₅: PRediction Model for gene Mutations. The PREMM 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, 2023).

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 v1.2024).

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 federal, state, or contractual requirements 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)
Multi-Gene Panel	
0101U	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatous 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)]

CPT Code	Description
Multi-Gene Panel	
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
81432	Hereditary Breast Cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53
81433	Hereditary Breast Cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11
81435	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11
81436	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); duplication/deletion analysis panel, must include analysis of at least 5 genes, including MLH1, MSH2, EPCAM, SMAD4, and STK11
81437	Hereditary neuroendocrine tumor disorders (e.g., medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); genomic sequence analysis panel, must include sequencing of at least 6 genes, including MAX, SDHB, SDHC, SDHD, TMEM127, and VHL
81438	Hereditary neuroendocrine tumor disorders (e.g., medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL

CPT Code	Description
Multi-Gene Panel	
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

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Description of Services

Genetic testing for hereditary cancer susceptibility is used to predict an individual's risk of cancer development in the future. It has been estimated that 5-10% 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 v1.2024).

To identify if 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 an individual has 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 1.2024). 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).

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 v1.2024, NCCN, Genetic/Familial High-Risk Assessment: Colorectal v1.2023, NCCN, Prostate Cancer v4.2022)

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, 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, TP53
Prostate cancer	ATM, BRCA1, BRCA2, CHEK2, and HOXB13

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, 2020). 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 several types of cancer. Women who are found to have a harmful BRCA variant are significantly more likely to develop Breast or Ovarian Cancer by the time they are 70-80 years old (Breast Cancer: 55%-72% for BRCA1 and 45%-69% BRCA2; Ovarian Cancer: 39%-44% for BRCA1 11%-17% for BRCA2). 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, 2020, NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic v1.2024).

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 both within a single gene and across multiple genes related to increased cancer risks. 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 of these Panel tests also include low to moderate-risk genes that may result in the identification of gene mutations that are of unclear clinical significance, or which would not clearly direct an individual's medical management recommendations. 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 v1.2024; NCCN, Genetic/Familial High-Risk Assessment: Colorectal v1.2023; 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 BRCA2 can include targeted analysis 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. Duplication/deletion testing identifies variants in 11-13% of cases for BRCA1 and 2-3% for BRCA2 (Petrucci et al., 2023).

Several studies have shown that BRCA1 breast cancer is more likely to be characterized as triple negative. Studies have reported BRCA1 P/LP variants in 4.4% -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 v1.2024). A study of 54 women with triple-negative breast cancer aged 40 years or younger who were not considered candidates for BRCA testing because of the lack of a strong family history, showed five with BRCA1 mutations and one with a BRCA2 mutation (11% mutation prevalence) (NCI, 2020; Young et al., 2009). In a cohort of triple-negative breast cancer patients, Gonzalez-Angulo et al. (2011) found a 19.5% incidence of BRCA mutations. Median age was 51 years (27-83 years). The authors recommend that genetic testing be discussed with patients with triple-negative breast cancer.

Kolor et al. (2017) reviewed medical claims from 2009-2014 for BRCA testing and resulting interventions among women ages 18-64 with employer sponsored health care. They noted that BRCA testing increased 2.3 times in metropolitan and 3.0 times in non-metropolitan areas during the study period. Receipt of preventative services within 90 days of testing also varied between these regions, with the exception of mastectomy (6-10% of testers over the study period). Women were less likely to receive MRI of the breast in non-metropolitan areas (8.2% vs. 10.3%), as well as mammography (11.5% vs. 13.8%). Receipt of genetic counseling before or after testing was more common in the metropolitan group, but in both groups, an increase was seen over the study period from 5.3-8% in metropolitan areas and 3.8-5.2% in non-metropolitan areas. Over time, the disparities between the two groups were reduced, and the authors note that the implementation of the USPSTF guidelines and the availability of BRCA counseling and testing under the Affordable Care Act in September of 2010 may have influenced the increase in testing and the reduction in differences between the two groups. The highest rate of BRCA testing in the study was 332.5 women per 100,000 women aged 44-54 which is comparable to the estimated prevalence of *BRCA* mutations in the general US population.

The prevalence of BRCA1/2 large rearrangements (LRs) was investigated in 48,456 patients with diverse clinical histories and ancestries that were referred for clinical molecular testing for suspicion of HBOC. Prevalence data was analyzed for patients from different risk and ethnic groups. Patients were designated as high-risk (n = 25,535) if their clinical history predicted a high prior probability. For these patients, LR testing was performed automatically in conjunction with sequencing. Elective patients (n = 22,921) did not meet the high-risk criteria but underwent LR testing if BRCA1/2 sequencing indicated no known mutations. Overall BRCA1/2 mutation prevalence among high-risk patients was 23.8% versus 8.2% for the elective group. The mutation profile for high-risk patients was 90.1% sequencing mutations versus 9.9% LRs, and for elective patients, 94.1% sequencing versus 5.9% LRs. The authors noted that this difference may reflect the bias in high-risk patients 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 patients of different ancestries. LR mutations were significantly more common in Latin American/Caribbean patients (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 16 (53%) were in BRCA2. Patients diagnosed with breast cancer at age \leq 50 years were found to have a higher BRCA1/2 mutation prevalence than probands with breast cancer who were diagnosed at age $>$ 50 years (21.1% vs 6.9%). In patients 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 breast-pancreas cancer families, suggesting that both genes are associated with pancreatic cancer risk.

Almost 10% of women with breast cancer who are younger than age 50 have BRCA mutations. Most of the BRCA-positive women do not have personal or family histories of breast or ovarian cancer and are not of Ashkenazi Jewish ancestry. Using a simulation model, Kwon et al. (2010) evaluated six populations of women younger than 50 with breast cancer, looking at costs and health benefits. The results led the authors to conclude that testing women with triple-negative breast cancers who were younger than 50 years for BRCA mutations should be adopted into current guidelines for genetic testing.

Ferrone et al. (2009) looked at the prevalence of BRCA1 and BRCA2 in an unselected group of Jewish patients and compared patients with resected BRCA mutation-associated pancreatic adenocarcinoma (PAC) to PAC patients without mutations. Of the 187 Jewish patients who underwent resection for PAC, tissue was available for 145 patients. Founder mutations for BRCA1 and BRCA2 were identified in 5.5% of patients [two with BRCA1 (1.3%) and six with BRCA2 (4.1%)]. A previous cancer was reported by 24% (35 of 145) of patients with the most common sites being breast cancer (9 of 35; 74%) and prostate cancer (8 of 35; 23%).

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 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 the 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 2022) 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 3,162 women for the prevalence of pathogenic/likely pathogenic variants (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 PV/LPV 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 PV/LPV 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 with panel testing to determine the rate of non-BRCA mutations. Eight-five women were tested with a multigene panel and of those, 33 (38.8%) tested positive for a pathogen mutation: 9 BRCA1, 5 BRCA2, 5 ATM, 1 BARD1, 4 CHEK2, 1 MSH2, 1 MSH6, 2 PALB2, 1 PMS2, 1 PTEN and 3 TP53. Overall, 17.6% tested positive for a non-BRCA breast cancer predisposition gene.

Daly et al. (2020) provided an overview to NCCN breast and ovarian cancer susceptibility screening guideline updates and described the changes in the appropriate testing algorithms. The guidelines state that there is strong evidence that genes beyond BRCA1/2 confer markedly increased risk of breast and/or ovarian cancers, such as CDH1, PALB2, PTEN, and TP53. This change is significant enough to modify the “BRCA1/2 Testing Criteria” page to now be titled “Testing Criteria for High-Penetrance Breast and/or Ovarian Cancer Susceptibility Genes.” Additionally, the testing criteria is also reorganized into three sections: (1) testing is clinically indicated, (2) testing may be considered, and (3) low probability of testing results having documented clinical utility. The authors also stated that multigene testing may be considered for patients who tested negative for one syndrome, but the personal and/or family history is suggestive of another or a different inherited cancer syndrome. The other major updates for the guidelines include revisions to Ashkenazi Jewish ancestry testing criteria and pancreatic cancer screening.

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. For evaluation, 31 genes were selected for evaluation of the relationship between the gene and breast cancer, and 32 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 panel genes associated with an increased risk of triple-negative breast cancer (TNBC). A large cohort of patients was assembled and multi-gene panel testing for 21 genes in 8753 patients was performed by a clinical testing laboratory and testing for 17 genes in 2148 patients was conducted by a Triple-Negative Breast Cancer Consortium (TNBCC) of research studies. 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) tested 300 women who previously tested negative for BRCA1/2. All of the subjects met additional criteria including: a personal history of bilateral breast cancer; or a personal history of Breast Cancer and a first or second degree relative with ovarian cancer; or a personal history of ovarian, fallopian tube, or peritoneal carcinoma. The testing determined that 9% of women had pathogenic mutations and 8% had mutations in genes other than BRCA1/BRCA2. The researchers concluded that individuals with additional criteria may be candidates for additional 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 addressed the evidence supporting BRCA1/2 and other inherited breast cancer 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 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, as of 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 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 technology. This multigene testing process increases the likelihood of finding variants of unknown significance, and it also 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)

In 2017 practice bulletin 182 (reaffirmed 2019), ACOG recommended criteria for genetic evaluation of HBOC syndrome. These recommendations include women with the following:

- A close relative (mother, sister, daughter, grandmother, granddaughter, aunt, or niece) with a known BRCA mutation; or a first-degree or several close relatives that meet one or more of the criteria below; or a close relative with male breast cancer
- Personal history of the following:
 - Ovarian cancer
 - Breast cancer at age 45 years or less
 - Breast cancer and have 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 have two or more close relatives with breast cancer at any age or 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 have 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 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 including:

- Breast surgeons, genetic counselors, and other medical professionals knowledgeable in genetic testing can provide patient education and counseling, although when the patient’s history and/or test results are complex, referral to a certified genetic counselor or genetics professional may be useful
- 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 patients with a personal history of breast cancer
- Patients who had genetic testing previously may benefit from updated testing

- Genetic testing should be made available to patients without a history of breast cancer who meet NCCN guidelines. Unaffected patients should be informed that testing an affected relative first, whenever possible, is more informative than undergoing testing themselves
- Variants of uncertain significance (VUS) are not clinically actionable and are considered inconclusive. Patients 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 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 (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 a patient with ovarian cancer with a known gene variant should be offered counseling, evaluation and testing as well. Variants of uncertain significant 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 recommends 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 (Robson et al., 2015).

National Comprehensive Cancer Network (NCCN)

The NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic Cancer guidelines (v1.2024) 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, 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:

- Individual has any blood relative with a known P/LP variant in a cancer susceptibility gene
- Individual has previously tested negative with limited previous testing (e.g., single gene or absent deletion duplication analysis), meets testing criteria below, and desires multi-gene testing
- 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 Lynch syndrome testing criteria

Breast Cancer

For individuals with a personal or family history of breast cancer, testing for high-penetrance breast cancer susceptibility genes (BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11, and TP53) is clinically indicated in the following situations (also refer to general testing criteria above):

- Individual has a personal history of breast cancer with the following features:

- Diagnosed ≤ 50 years old; or
- 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
 - § Pathology/histology includes:
 - Triple-negative breast cancer; or
 - Multiple primary breast cancer (synchronous or metachronous) at any age; or
 - Lobular breast cancer with personal or family history of diffuse gastric cancer
 - § Individual has male breast cancer
 - § Individual is of Ashkenazi Jewish ancestry
 - § Individual has at least one close blood relative with
 - Breast cancer at age 50 or younger; or
 - Male breast cancer; or
 - 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 has a family history of cancer
 - Individual is affected with breast cancer but does not meet criteria above or individual is unaffected with breast cancer 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); or
 - Individuals affected or unaffected with breast cancer who do not meet the criteria above but have 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 59 or younger and does not meet any of the above criteria but approaches a 2.5% probability of having a P/LP variant. *Caution: The majority of those 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 particularly 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 affected or unaffected with breast cancer who otherwise does not meet any of the above criteria but with a 2.5%–5% probability of BRCA1/2 P/LP variant based on prior probability models (e.g., Tyrer-Cuzick, BRCAPro, CanRisk)

There is a low probability (less than 2.5%) that testing will identify high-penetrance genes in the following situations:

- Female diagnosed with breast cancer at greater than 60 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 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 [ATM, BRCA1, BRCA2, BRIP1, Lynch syndrome genes (MLH1, MSH2, MSH6, EPCAM), PALB2, RAD51C, and RAD51D] is clinically indicated in the following situations (also refer to general testing criteria above):

- Individual has a personal history of epithelial ovarian cancer (including fallopian tube or peritoneal cancer) diagnosed at any age
- Individual has family history of cancer only
 - Individual has a first- or second-degree blood relative with epithelial ovarian cancer (including fallopian tube or peritoneal cancer) at any age; or
 - 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 [ATM, BRCA1, BRCA2, CDKN2A, Lynch syndrome genes (MLH1, MSH2, MSH6, EPCAM), PALB2, STK11, and TP53] is clinically indicated in the following situations (also refer to general testing criteria above):

- Individual has a personal history of exocrine 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 (*ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *HOXB13*) is clinically indicated in the following situations (also refer to 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; or
 - Individual has ancestry/family history including:
 - § At least one close blood relative with:
 - Breast cancer diagnosed age 50 or younger; or
 - Triple negative breast cancer at any age; or
 - Male breast cancer at any age; or
 - Ovarian cancer at any age; or
 - Pancreatic cancer at any age; or
 - Metastatic high- or very-high risk group prostate cancer at any age
 - § At least two close blood relatives with breast cancer or prostate cancer diagnosed at any age
 - § Ashkenazi Jewish ancestry

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/cirbriform histology.

National Society of Genetic Counselors (NSGC)

In their 2017 position statement (reaffirmed 2023), the NSGC provides endorsement for the use of multi-gene panel tests 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 stress 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 members
- Review of issues related to genetic discrimination

The U.S. Preventive Services Task Force (USPSTF)

In 2019, the U.S. Preventive Services Task Force (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 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) (USPSTF, 2019).

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 10 genes. The participants were largely female (60.7%), White (70.6%) and 50 years of age or older (68.9%). A total of 4,864 individuals (14.2%) were found to have one or more P/LP germline variants and 3,111 (9.1%) had a variant that is associated with increased CRC/polyposis risk. Another 3.1% had an otherwise clinically actionable P/LP variant. Notably, there was not a clear association 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%. VUSs 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 and 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 next-generation sequencing platform to perform testing 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% ($n = 34$) of participants had clinically actionable findings that would not have been detected with a CRC specific gene panel or if standard clinical practice criteria had been followed. Overall, 11% (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 colorectal cancer syndromes, specifically around multi-gene cancer panels for hereditary colorectal cancer syndromes. For polyposis syndromes that include FAP, attenuated FAP (AFAP), MAP, and other rare genetic causes of multiple adenomatous polyps, data suggested that there are many genes that may contribute to the CRC risk including: *AXIN2*, *GREM1*, *NTHL1*, *POLE*, *POLD1*, and *MSH3*. Likewise, there are many genes that have been associated with Lynch syndrome which yields an increased risk for colon cancer, endometrial and ovarian cancers, as well as gastric, pancreatic, biliary tract, ureter and renal pelvis, small intestine, and brain (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 Lynch syndrome and manage the

future risk of CRC or endometrial cancer. The panel recommends universal screening of all patients with CRC or endometrial cancer at any age with tumor showing evidence of MMR deficiency, either by MSI or loss of MMR protein expression.

Using the ClinGen Clinical Validity framework, Seifert et al. (2019) evaluated gene-disease associations in hereditary colorectal cancer. This study assessed 42 gene-disease pairs. Of all gene-disease pairs evaluated, 14/42 (33.3%) were Definitive, 1/42 (2.4%) were 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 only < 60% of genes on available panels have Strong or Definitive evidence of association.

Martin-Morales et al. (2018) used a NGS panel to find genes that were involved in families that fulfill the clinical criteria for Lynch syndrome but lack the germline mutations. For this study, 98 patients from these families were tested with a multi-gene panel targeting 94 genes involved in cancer predisposition. The mutations identified were validated by Sanger sequencing. The study identified 19 likely pathogenic variants in 18 patients and out of these 19, 8 were found in MMR genes (5 in MLH1, 1 in MSH6 and 2 in PMS2). Additionally, 11 mutations were detected in other genes, including high penetrance genes (APC, SMAD4 and TP53) and moderate penetrance genes (BRIP1, CHEK2, MUTYH, HNF1A and XPC). Novel mutations including c.1194G > A in SMAD4, c.714_720dup in PMS2, c.2050T > G in MLH1 and c.1635_1636del in MSH6 were detected. The researchers concluded that the detection of new pathogenic mutations in high and moderate penetrance genes could contribute to the explanation of the heritability of colorectal cancer.

Clinical Practice Guidelines

American College of Gastroenterology (ACG)

The ACG published recommendations for the management of patients with hereditary gastrointestinal cancer syndromes, including genetic testing recommendations (Syngal et al., 2015). The authors note that genetic testing is widely available and should be part of standard of care of patients 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 patients with more than one genetic syndrome on the differential diagnosis list, as testing for multiple conditions at once can decrease costs and be time efficient when compared to sequentially screening the possible list of genes. It is additionally noted, however, that even though there might be time 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 variants of unknown significance 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. 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 may be 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 colorectal cancer (CRC) and individuals with polyposis, multigene panel testing has been accepted, however the genes included on the panels are often widely varied. The Collaborative Group of the Americas on Inherited Gastrointestinal Cancer Position Statement Committee performed an evidence review to create on 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 some updated genetic testing criteria. The collaborative group highlighted the following genes associated with Lynch Syndrome (LS): MLH1, MSH2, MSH6, PMS2, EPCAM and the genes associated with polyposis syndromes: APC, BMP RIA, MUTYH, PTEN, and STK11. These genes were noted as the minimum genes that should be included on a multigene panel for these conditions. The group also recommended individuals who should undergo multigene panel testing including:

- Colorectal cancer diagnosed age < 50 years
- Multiple LS primary tumors
- Colorectal cancer and at least one first degree relative with colorectal or endometrial cancer
- PREMM5 score \geq 2.5% or MMRpro or MMRpredict score \geq 5%
- Mismatch repair-deficient colorectal cancer, not attributed to MLH1 promoter methylation
- Individuals meeting any other genetic testing criteria
- \geq 10 cumulative colorectal adenomas
- \geq 3 cumulative gastrointestinal hamartomatous polyps

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

In 2022, CGA-IGC and NSGC published a practice resource addressing genetic evaluation of Lynch syndrome (Holter et al., 2022). They note that the term Lynch syndrome should only be used when individuals have been identified to have germline heterozygous pathogenic/likely pathogenic (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 Lynch syndrome:

- Family history of a known germline MMR pathogenic/likely pathogenic variant
- Personal history of CRC or EC with any of the following characteristics:
 - Age of diagnosis < 50 years; or
 - Tumor is dMMR: MSI-high or abnormal MMR IHC; or
 - Another LS-related cancer*; or
 - Family history of LS-related cancers in first or second-degree relatives
 - § ≥ 1 relative(s) diagnosed at age < 50; or
 - § ≥ 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; or
 - ≥ 1 first-degree relative(s) with > 1 diagnoses of LS-related cancers; or
 - ≥ 2 or more first-or second-degree relatives with LS-related cancers with ≥ 1 diagnosed age < 50; or
 - ≥ 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., PREMM5, MMRpro)

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

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines present evidence-based criteria for genetic testing for hereditary high-risk colorectal cancer syndromes caused by a variety of genes (NCCN, Genetic/Familial High-Risk Assessment: Colorectal v1.2023). The guidelines address genetic risk assessment, counseling, testing, and management based on test results and indicate that multigene panel testing for Lynch syndrome and other cancer risk genes should include, at a minimum, the following CRC-related genes: APC, MUTYH, MLH1, MSH2, MSH6, PMS2, EPCAM, BMPR1A, SMAD4, PTEN, STK11, and TP53. Use of panels including genes beyond those above should be based on an individual's personal and family history of cancer in addition to patient/provider preference. The guidelines indicate that the germline multigene panel testing strategy is an alternative to selection of individuals with CRC for genetic evaluation because it has higher sensitivity for detecting individuals with LS and other cancer risk genes than the strategy of selection of germline testing based on specific family history and tumor-based criteria.

Lynch Syndrome Testing Criteria

Testing is recommended when:

- Known LS pathogenic variant in the family
- Individual has LS-related cancer and any of the following:
 - Diagnosed at 49 years or younger; or
 - Diagnosed with a synchronous or metachronous LS-related cancer at any age; or
 - Has a first- or second-degree relative with an LS-related cancer diagnosed at 49 years of age or younger; or
 - 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 colorectal or endometrial cancer diagnosed at 49 years of age or younger; or
 - One or more first-degree relatives with a colorectal or endometrial cancer and a synchronous or metachronous LS-related cancer at any age; or
 - Two or more first- or second-degree relatives with LS-related cancers including one or more diagnosed at age 49 or younger; or
 - Three or more first-or second-degree relatives with LS-related cancers at any age
- Individual with an increased model-predicted risk for Lynch syndrome associated cancers
 - Individual has a ≥ 5% risk of MMR gene pathogenic variant based on predictive models

- § Individuals with personal history of CRC and/or endometrial cancer with a PREMM5 score of 2.5% or greater should be considered for multigene panel testing; or
- § Individuals with no personal history of CRC and/or endometrial cancer may use a PREMM5 score of $\geq 2.5\%$ rather than $\geq 5\%$ to select individuals for MMR testing, when used with clinical judgement
- Personal history of a tumor with a mismatch repair (MMR) deficiency or immunohistochemistry (IHC) diagnosed at any age

Adenomatous Polyposis Testing Criteria

Testing is recommended when:

- Individual has a personal history of twenty or more cumulative adenomas; or
- Family history of a known P/LP variant in polyposis genes; or
- Individual has multifocal/bilateral congenital hypertrophy of retinal pigment epithelium (CHRPE)

In addition, testing may also be considered if:

- Individual has a personal history of a desmoid tumor, hepatoblastoma, 121 cribriform-morular variant of papillary thyroid cancer, unilateral CHRPE; or
- Individual meets criteria for SPS and has at least some adenomas; or
- Individual has a personal history of between 10 and 19 cumulative adenomas; or
- There is a family history of polyposis and family is unwilling or unable to undergo testing

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

The guideline further notes that commercially available multi-gene tests may be significantly different, varying in 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.

The US Multi-Society Task Force on Colorectal Cancer (USMSTF)

The USMSTF is a group of colorectal cancer (CRC) content experts chosen by the American Gastroenterological Association (AGA), American College of Gastroenterology (ACG), and American Society for Gastrointestinal Endoscopy (ASGE), 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: 2 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 multigene panel test. (Strong recommendation, low quality of evidence)
- Genetic evaluation should be performed for any individual with the following: 1) 2 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) 5 or more juvenile polyps of the colon or rectum; or 2) 2 or more juvenile polyps in other parts of the gastrointestinal tract; or (3) any number of juvenile polyps and 1 or more first-degree relatives 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 HHT at the time of the diagnosis, including screening for and appropriate management of cerebral and pulmonary AVMs. (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

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 multisynndrome panel testing to assist with clinical management of individuals with a

suspected hereditary cancer syndrome. Four clinical studies addressing multisynndrome panel testing were identified, but none compared the use of comprehensive multisynndrome 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 1,727 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 inconclusive rate which supports the use of universal testing of all individuals with PPGL, regardless of tumor type, age of onset, metastatic disease, syndromic features, family history or functional status, supporting the use of concurrent MGPT as the preferred method of testing.

Nölting et al. (2022) published a review integrating current guidelines and expert opinions regarding the personalized management of pheochromocytoma and paraganglioma. Pheochromocytomas and paragangliomas have the highest rate of heritability among all tumors with approximately 30% to 35% of Caucasian individuals (lesser percentage in Chinese population) showing germline mutations. In addition 35% to 40% of Caucasians (higher still 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 of 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 next-generation sequencing 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 a > 80 gene next-generation sequencing (NGS) panel to perform germline sequencing on 250 individuals with pancreatic cancer (PC). Included individuals were not selected for family history of cancer or age. Pathogenic germline variants (PGVs) were found in 15.2% of participants, with 2 participants testing positive for more than one PGV. Variants of uncertain significance (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 PC were carriers of PGV. The authors recommend that multigene germline testing should be used in individuals with PC 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 pathogenic germline variants (PGVs) in cancer patients using a universal approach rather than targeted testing based on clinical practice guidelines. A total of 2984 patients with solid tumor cancers were studied. Patients were not selected based on cancer type, disease state, family history, age, or ethnicity. Patients received germline sequencing using next-generation sequencing (NGS) with greater than 80 genes tested. The researchers were looking to compare this universal strategy to the standard guideline-directed approach and uptake of cascade family variant testing. PGVs were detected in 397 participants (13.3%), and 1415 patients (47.4%) were found to have variants of uncertain significance. Clinically actionable findings that would not have been detected by family history or phenotype-based testing criteria were identified in 192 patients. Of the patients with high-penetrance PGV, modifications in treatment were made for 42 patients. Individuals with a younger age of diagnosis (mean age was 61.4 years) were associated with presence of PVG, and only 70 patients total (17.6%) of individuals with PGVs had members of their family undergoing FVT. The authors concluded that the universal multigene panel testing of patients with 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 death, and the 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 multigene panel testing for hereditary cancers. The cohort consisted of 165,000 patients referred for multigene panel testing, and the researchers assessed phenotype-specific pathogenic variant (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). Patients with ovarian cancer had the highest PV frequencies (13.8%). Fewer than half of PVs identified were in patients that met the testing criteria for only *BRCA1/2* (33.1%) or only Lynch syndrome (46.2%). For patients that did not meet the testing criteria, 5.8% had PVs in *BRCA1/2* and 26.9% had PVs in Lynch syndrome.

Muth et al. (2019) discussed pheochromocytoma (PCC) and paraganglioma (PGL), which are rare tumors stemming from the chromaffin cells in the adrenal medulla (PCC) or the sympathetic or parasympathetic extra-adrenal paraganglia (PGL), 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 PCC and PGL are part of hereditary syndromes and approximately 20% of hereditary PCC and PGL 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 PGL 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 were tested with a 27-gene inherited cancer panel and 84% had a family history of cancer. Of these individuals, 65 were determined to have variants classified as pathogenic or likely pathogenic across 14 genes (10.3%). Only 42% of these variants occurred in classic HBOC or Lynch Syndrome-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.

Giri et al. (2018) reported on a consensus conference for prostate cancer where the goal was to determine the appropriate genetic testing routes. Seventy-one experts participated in the panel and determined that testing of *HOXB13* for suspected hereditary prostate cancer was considered to have high grade evidence. Similarly, *BRCA1/2* mutations being linked to prostate cancer also provided high grade evidence. The evidence the panel reviewed for DNA mismatch repair genes for suspected Lynch syndrome to prostate cancer risk was considered moderate grade. Both *ATM* and *NBN* mutations were considered to be emerging but not quite moderate grade. Other genes on many panels were determined to have low or insufficient data to determine the prostate cancer risk. The authors conclude that additional research is needed to develop more appropriate definitions for hereditary prostate cancer genetic testing.

Rednam et al. (2017) discussed the genes related to hereditary paraganglioma and pheochromocytoma syndrome in their 2017 publication on Von Hippel-Lindau and hereditary PCC and PGL syndromes. Genes related to hereditary paraganglioma and pheochromocytoma include the SDHx genes, *MAX*, *TMEM127* and potentially *HIF2 α* , *EGLN1*, and *KIF1 β* 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 PCC and PGL are hereditary and diagnosis is based on molecular genetic testing which should be offered to any individual with PCC or PGL.

An analysis of 252,223 individuals by a 25-gene pan-cancer panel was performed by Rosenthal et al. (2017). Of these individuals, the majority (92.8%) met testing criteria for HBOC and/or Lynch syndrome (LS). Pathogenic variants were identified in 6.7% of the tested individuals with *BRCA1/2* (42.2%), other breast cancer (BR) genes (32.9%), and the LS genes (13.2%). However, half of the pathogenic variants 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 pathogenic variants over single-syndrome testing.

Bholah and Bunchman (2017) published a review of the literature regarding neuroendocrine tumors pheochromocytoma (PCC) and paraganglioma (PGL) in which they demonstrated that the generally accepted concept of 10% of cancers are inherited may not apply to PCC and PGL. They noted that the European-American-Pheochromocytoma-Paraganglioma-Registry (EAPPR) has released data that 80% of individuals in their registry had a germline mutation, and smaller series of reports gave a germline mutation prevalence of 30-40%. Genes that are involved in PCC and PGL include genes responsible for 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 PGL-PCC syndromes with varying penetrance.

A retrospective study by Babic et al. (2017) analyzed pediatric pheochromocytomas and paragangliomas to determine the role of genetic testing. Of 55 patients, 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 pheochromocytomas and paragangliomas likely have detectable germline mutations and thus, genetic testing may be helpful to guide treatment.

Pilié et al. (2017) used a multi-gene panel to sequence germline DNA from 102 men with prostate cancer and at least one additional primary cancer who also met one of three additional criteria. The researchers identified over 3500 variants including deleterious or likely pathogenic germline mutations in 11 of the 102 men (10.8%) of men. Eight of the men had germline variants in 1 of 6 cancer predisposition genes including BRCA2 (three cases), ATM (two cases) and one case in MLH1. The researchers concluded that men with prostate cancer and at least 1 additional primary cancer may have a germline deleterious mutation.

In October of 2016, the American Association of Cancer Research (AACR) held the Childhood Cancer Predisposition Workshop. International experts in care of children with a hereditary risk of cancer met to define surveillance strategies and management of children with cancer predisposition syndromes. Several consensus publications resulted. Achatz et al. (2017) focused on inherited polyposis gastrointestinal syndrome cancers of childhood, and published consensus guidelines established by their expert panel from the workshop, which included recommendations on genetic testing strategies. They noted that children at risk for an inherited polyposis syndrome are typically identified in two ways; through family history, because a close family member has been diagnosed and second, because the child has symptoms. In the first clinical scenario, the expert panel recommends first testing the affected blood relative in order to ensure that highly accurate and actionable results are available for the family. Genetic testing in the child should be only for the familial pathogenic variant, and not take place until 1 year before the age at which the first surveillance action would occur. This allows time for coordination of genetic counseling and testing. In the second scenario, when the child presents with symptoms, genetic testing should be targeted for the gene most likely to be causative, when possible. For example, if the presenting symptom is congenital hypertrophy of the retinal pigment epithelia (CHRPE) associated with familial adenomatous polyposis (FAP), testing should be for the *APC* gene. This will help assure high specificity with fewer variants of unknown significance or unanticipated findings. The expert panel noted, however, that many of these disorders have broad, overlapping clinical presentations and in some cases, when clinical features cannot identify the most likely syndrome, a multi-gene hereditary cancer panel may be time efficient and cost effective in identifying a causative variant. The expert panel cautions that the larger the panel, the more likely it is that a variant of unknown significance will be found, and the chance of identifying an incidental, adult-onset disorder goes up. Genetic counseling is highly recommended.

Druker et al. (2017) reported on genetic counselor recommendations for testing and surveillance for pediatric cancers from the 2016 AACR Childhood Cancer Predisposition Workshop. The authors note that with the advent of NGS technology, it is increasingly common for patients with childhood cancer to undergo somatic genetic testing of their tumor, or undergo germline testing using large gene sequencing panels, genome-wide chromosomal microarrays, and/or whole exome/genome sequencing. Given the lack of guidelines for genetic counseling and testing in the pediatric cancer population, the authors provide expert consensus recommendations for when to refer to pediatric cancer genetics clinics, pretest counseling and informed consent and assent for cancer genetic testing of children, test selection and timing of testing, posttest counseling, and psychosocial aspects of cancer surveillance for children with hereditary cancer syndromes. It is recommended that the child and family be referred to genetic counseling at the time that the tumor is diagnosed, or germline genetic testing is being considered. When considering a genetic testing, the clinician should consider the clinical presentation and family history to determine whether to order a test for a familial variant or a broader panel. The authors recommend that when a family pathogenic variant is known, the test ordered should be only for that variant. They note that this is the least expensive and most efficient approach, and if possible, the same lab the identified the mutation in the initial family member should be use. When the patient's presentation clearly fits a specific syndrome, only the gene(s) for that specific syndrome should be tested. This ensures the greatest specificity and reduces the risk of a variant of unknown significance. When a patient presents with symptoms that can be explained by multiple syndromes, a multi-gene hereditary cancer panel can be considered. This increases the chance that a causative variant will be identified. However, it also increases the chance that a variant of unknown significance will be identified, as well as variants in moderate-risk genes for which limited surveillance or clinical management

recommendations may be available. Finally, whole exome or genome sequencing should be considered for those with multi-system phenotypes, those with negative multi-gene panel results, and for those wanting to participate in research. The limitations noted with whole exome or genome sequencing include, but are not limited to, inconsistent coverage of genes of interest, inconsistent coverage of copy number variants, the greatest chance of finding variants of unknown significance or incidental findings, and challenges in storing and reinterpreting data. Finally, the clinician should ensure that the test ordered includes the gene(s) of interest, the testing methodology and variant interpretation have been well validated, should understand the labs reinterpretation practices, cost, turnaround time, and the laboratory's policies regarding data sharing.

Hermel et al. (2017) described the experience of a rural Familial Cancer Program implementing multi-gene panel testing. They conducted a retrospective review of patients undergoing panel testing between May 2011 and August 2015. A total of 236 patients were identified. Seven were denied testing by insurance, and two cancelled, leaving 227 patients who completed the process. Patients were at risk for hereditary cancer syndromes based on personal or family history. Most, 84%, had a personal history of cancer, and 25% had multiple primary tumors. Breast Cancer was most common in 80% of patients with single primary tumors, followed by 16% with a history of polyps with 8% had a concomitant history of cancer. About 20% of patients had already had either BRCA1/2 or MSH2 testing prior to the multi-gene panel. Sixty-seven patients had reportable finding. Twenty-eight, 12%, had a pathogenic variant identified in one of the following genes: PLAB2, ATM, BARD1, CDKN2A, CHEK2, GALNT12, NBN, PMS2, APC, BRCA1, BRCA, or MUTYH. Forty-four patients, 19%, had a variant of unknown significance (VUS), and five had both a pathogenic variant and a VUS. An additional three patients had two VUS. Of the patients with a pathogenic variant, 36%, representing 4% of the overall cohort had a variant in a highly penetrant gene with an odds ratio over 5 for organ specific cancer.

Nguyen et al. (2017) published a retrospective review of the use of a 19 gene hereditary cancer panel in patients diagnosed with kidney cancer. Patients were tested at a commercial laboratory from August 2013 to June 2016. Clinical characteristics such as age, gender, age of diagnosis, ordering institution, kidney cancer histology, personal history and cancer history were obtained from test requisitions. In total, 1235 patients 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 patients and common tumor histology such as clear cell, papillary and chromophobe kidney tumors was present in 67% of these individuals. The remainder reported less common and mixed histology. Overall, 859 had only kidney cancer, and 283 had an additional primary cancer, and 93 had more than two primary cancers. A positive family history for cancer was reported in 1007 patients, and of these, 369 reported a family history of kidney cancer. Half of all cases were referred by university-based hospitals, 44% from non-university hospitals, 4.5% from private practice clinicians. Genetics providers referred 81% of cases, oncologists 14%, non-oncology physicians 1%, and other healthcare providers referred the remainder. Overall, 6.1% had a pathogenic variant identified, 18% had a variant of unknown significance, 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 variants of unknown significance (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)

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?" and 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 a patient 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 variants of unknown significant, it is recommended that

providers with particular expertise in cancer risk assessment should be involved in the ordering and interpretation of multi-gene panels, 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).

National Comprehensive Cancer Network (NCCN)

Prostate Cancer

NCCN Practice Guidelines for Prostate Cancer (v4.2023) indicate that germline testing, which should include at least BRCA1, BRCA2, ATM, PALB2, CHEK2, HOXB13, MLH1, MSH2, MSH6, and PMS2 is recommended for individuals with a personal history of prostate cancer in the following scenarios:

- Individual has metastatic, regional (node positive), very-high risk localized, high-risk localized prostate cancer
- Individual has a personal history of breast cancer
- Individual has a family history and/or ancestry including at least one of the following:
 - One or more first-, second-, or third-degree relative with:
 - § Breast cancer at 50 years of age or younger; or
 - § Colorectal or endometrial cancer at 50 years of age or younger; or
 - § Male (sex assigned at birth) breast cancer, ovarian, exocrine pancreatic or metastatic, regional, very-high-risk, high-risk prostate cancer at any age
 - One or more first-degree relatives (parent or sibling) with prostate cancer at ≤ 60 years of age; or
 - Two or more first-, second-, or third-degree relatives with breast or prostate cancer at any age; or
 - Three or more first- or second-degree relatives with Lynch syndrome-related cancers, especially if diagnosed younger than 50 years of age (colorectal, endometrial, gastric, ovarian, exocrine pancreas, upper tract urothelial, glioblastoma, biliary tract, and small intestinal cancer); or
 - A known family history of familial cancer risk mutation (P/LP variants), especially in: BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6, PMS2, or EPCAM; or
 - Ashkenazi Jewish ancestry

Germline testing may be considered for individuals with a personal history of prostate cancer in the following scenarios:

- Intermediate-risk prostate cancer with intraductal/ciribriform histology diagnosed at any age
- Prostate cancer AND a prior personal history of any of the following cancers: exocrine pancreatic, colorectal, gastric, melanoma, upper tract urothelial, glioblastoma, biliary tract, and small intestinal

Pancreatic Adenocarcinoma

NCCN Clinical Practice Guidelines for Pancreatic Adenocarcinoma (v2.2023) recommend genetic testing for inherited mutations for any individual with confirmed pancreatic cancer using comprehensive gene panel tests for hereditary cancer syndromes. In addition, genetic counseling is recommended for individuals who test positive for a pathogenic mutation (ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, and TP53) or for individuals with 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 (v1.2023) address genetic counseling and testing for individuals with pheochromocytomas and paragangliomas, stating that growing evidence indicates that pheochromocytomas and paragangliomas may be associated with inherited genetic syndromes. Pheochromocytomas have occurred in patients with MEN2A, MEN2B, and other familial diseases such as neurofibromatosis and von Hippel Lindau (VHL) syndrome. Polycythemia-paraganglioma-somatostatinoma syndrome related to somatic mutations in the HIF2A gene is associated with paragangliomas. In addition to germline variations associated with these syndromes (i.e., RET, NF1, VHL), germline variations in SDHB, SDHA, SDHAF2, SDHD, SDHC, TMEM127, MAX, FH, and MDH2 have also shown an association with increased occurrence of pheochromocytomas and paragangliomas. Genetic counseling, with genetic testing when appropriate, is recommended in patients with a pheochromocytoma or paraganglioma and in those with a family history of these tumors, since a substantial proportion of these individuals are likely to have a heritable mutation. Counseling and potentially, testing, should be performed in those with a family history of these tumors as well.

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 multi-gene hereditary cancer panels. The quality of the studies was low due to small study populations, short follow-up, 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. The study then assessed the utility of this splicing profile on 1000 patients with suspected hereditary cancer syndromes. The RNA testing coupled with DNA testing was performed and the RNA testing identified seven patients with pathogenic mutations 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 patients with inconclusive variants after DNA testing to determine if RNA testing improved the data. The study included patients and/or families with hereditary breast and ovarian cancer, Lynch syndrome, 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 patient results that had only undergone DNA testing and the researchers determined that 7,265 of these had inconclusive variants that affect splicing. Overall, considering the previous study, approximately 1 in 43 individuals could benefit from RNA testing. The researchers call out several limitations, including patient 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 August 31, 2023)

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Policy History/Revision Information

Date	Summary of Changes
04/01/2024	<p>Coverage Rationale</p> <ul style="list-style-type: none"> ● Revised coverage guidelines for the following services to indicate: <ul style="list-style-type: none"> ○ Individuals with a Personal History of a Primary Solid Tumor Cancer <ul style="list-style-type: none"> ○ 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 following criteria are met: <ul style="list-style-type: none"> § Individual has a personal history of at least one of the following: <ul style="list-style-type: none"> – 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 is a cisgender, transgender, or gender-diverse individual assigned male at birth – Breast Cancer and unknown or Limited Family History – Breast Cancer and at least one first- or second-degree relative with a BRCA-Related Cancer – Ovarian Cancer, fallopian tube cancer, and/or primary peritoneal cancer – Pancreatic cancer – Metastatic prostate cancer – Cancer Associated with Lynch Syndrome – Paraganglioma or pheochromocytoma – At least two different Primary Solid Tumor cancers (excluding basal or squamous cell skin cancer) § Individual has a personal history of a Primary Solid Tumor cancer (excluding basal or squamous cell skin cancer) and a family history of cancer which includes at least one of the following: <ul style="list-style-type: none"> – 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 cancer (excluding basal or squamous skin cancer) § Individual has a personal history of a Primary Solid Tumor cancer (excluding basal or squamous cell skin cancer) and at least one of the following:

Date	Summary of Changes
	<ul style="list-style-type: none"> - A BRCA1/2 pathogenic variant was detected in tumor tissue - Tumor tissue testing demonstrated that the cancer was MSI-high or had immunohistochemical staining showing the absence of one or more mismatch repair 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 PREMM5, MMRpro, or MMRpredict Score of 2.5% or greater for having a Lynch syndrome gene mutation <p>Individuals with No Personal History of a Primary Solid Tumor Cancer</p> <ul style="list-style-type: none"> o 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 cancer (excluding basal or squamous cell skin cancer) is proven and medically necessary if at least one of the following criteria are met: <ul style="list-style-type: none"> § At least one first degree relative with a history of at least one of the following: <ul style="list-style-type: none"> - Two or more different Primary Solid Tumor cancers (excluding basal or squamous cell skin cancer) - Cancer Associated with Lynch Syndrome - Paraganglioma or pheochromocytoma § At least one first- or second-degree relative with a history of at least one of the following: <ul style="list-style-type: none"> - Breast Cancer diagnosed at age 50 or younger - Metastatic prostate cancer - Ovarian Cancer, fallopian tube cancer, and/or primary peritoneal cancer - Pancreatic cancer § At least one second-degree relative with a history of at least one of the following: <ul style="list-style-type: none"> - Two or more Cancers Associated with Lynch Syndrome - Cancer Associated with Lynch Syndrome diagnosed at age 50 or younger § Family history includes at least one of the following: <ul style="list-style-type: none"> - 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 cancer (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 § A personal history of colorectal polyposis with at least ten adenomas § Any of the following: <ul style="list-style-type: none"> - Individual has a Tyrer-Cuzick, BRCAPro, or Penn11 Score of 5% or greater for a BRCA1/2 pathogenic variant - Individual has a PREMM5, MMRpro or MMRpredict Score of 5% or greater for having a Lynch syndrome gene mutation <p>Definitions</p> <ul style="list-style-type: none"> • Updated definition of: <ul style="list-style-type: none"> o BRCA-Related Cancers o High Penetrance Breast Cancer Susceptibility Genes o Limited Family History o Multi-Gene Panel o Ovarian Cancer o Triple-Negative Breast Cancer • Removed definition of “Panel”

Date	Summary of Changes
	<p data-bbox="337 138 643 172">Supporting Information</p> <ul data-bbox="337 176 1458 270" style="list-style-type: none"> <li data-bbox="337 176 1458 237">• Updated <i>Description of Services</i>, <i>Clinical Evidence</i>, and <i>References</i> sections to reflect the most current information <li data-bbox="337 241 899 270">• Archived previous policy version CS049KY.09

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state, or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state, or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state, or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state, or contractual requirements for benefit plan coverage. 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.

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