Genetic Testing for Hereditary Cancer

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Instructions for Use

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Application

UnitedHealthcare Commercial

This Medical Policy applies to all UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit plans in all states except for Colorado.

Coverage Rationale

Pre-test genetic counseling is strongly recommended in order to inform persons being tested about the advantages and limitations of the test as applied to a unique person.

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

Hereditary Breast and Ovarian Cancer Panel Testing

Genetic testing Panels for High Penetrance Breast Cancer Susceptibility Genes **are proven and medically necessary for individuals with a personal history of a** BRCA-Related Cancer **for any of the following indications**:

- Personal history of Breast Cancer and at least one of the following:
  - Diagnosed at age 50 or younger
  - Metastatic Breast Cancer diagnosed at any age
  - Multiple primary Breast Cancers diagnosed at any age (prior diagnosis or bilateral cancer)
  - Triple negative Breast Cancer diagnosed at any age
  - Lobular Breast Cancer diagnosed at any age with a personal or family history of diffuse gastric cancer diagnosed at any age
  - Ashkenazi Jewish ancestry
  - Cisgender, transgender, or gender-diverse individual assigned male at birth

    - Unknown or Limited Family History
    - At least one first- or second-degree relative with a BRCA-Related Cancer
- Personal history of one of the following cancers at any age:
    - Ovarian Cancer
    - Pancreatic cancer
    - Metastatic prostate cancer
- A BRCA1/2 pathogenic variant detected in tumor tissue
- Individual has a Tyrer-Cuzick, BRCAPro or Penn11 Score of 2.5% or greater for a BRCA1/2 pathogenic variant

Genetic testing Panels for High Penetrance Breast Cancer Susceptibility Genes **for individuals with no personal history of a** BRCA-Related Cancer **are proven and medically necessary for any of the following indications:**

- At least one first- or second-degree relative with a BRCA-Related Cancer; or
- Ashkenazi Jewish ancestry and at least one Close Blood Relative with a BRCA-Related Cancer; or
- Individual has a Tyrer-Cuzick, BRCAPro or Penn11 Score of 5% or greater for a BRCA1/2 pathogenic variant

Genetic testing Panels for High Penetrance Breast Cancer Susceptibility Genes **are unproven and not medically necessary for all other indications including:**

- Screening for cancer risk for individuals not listed in the proven indications above; or
- Risk assessment of other cancers; or
- Confirmation of direct-to-consumer genetic testing without meeting any of the proven indications above

Other Hereditary Cancer Syndrome Multi-Gene Panel Testing

Genetic testing with a Multi-Gene hereditary cancer Panel **for individuals with a personal history of a** Primary Solid Tumor **cancer (excluding basal or squamous cell carcinoma) is proven and medically necessary if the following criteria are met:**

- The suspected hereditary cancer syndromes can be diagnosed by testing two or more genes included in the specific hereditary cancer Panel; and
- At least one of the following:
    - A personal history of at least two different primary solid tumor cancers (excluding basal or squamous cell carcinoma); or
    - A personal history of BRCA-Related Cancer diagnosed at age 40 or younger; or
    - A personal history of BRCA-Related cancer and at least one Close Blood Relative with a Cancer Associated with Lynch Syndrome; or
    - At least one Close Blood Relative diagnosed with a BRCA-Related Cancer at age 40 or younger; or
    - 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 carcinoma); or
    - A personal history of paraganglioma or pheochromocytoma; or
    - A personal history of Cancer Associated with Lynch Syndrome; or
    - A personal history of cancer where tumor testing results demonstrate 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); or
    - A personal history of colorectal polyposis with at least 10 adenomatous polyps, at least 2 hamartomatous polyps or at least 5 serrated polyps/lesions proximal to the rectum; or
    - Individual has a PREMM5, MMRpro or MMRpredict Score of 2.5% or greater for having a Lynch syndrome gene mutation

Genetic testing with a Multi-Gene hereditary cancer Panel **for individuals with no personal history of a** Primary Solid Tumor **cancer is proven and medically necessary if the following criteria are met:**

- The suspected hereditary cancer syndromes can be diagnosed by testing two or more genes included in the specific hereditary cancer Panel; and
- At least one of the following:
    - At least one first-degree relative diagnosed with at least two different primary solid tumor cancers (excluding basal or squamous cell carcinoma); or
    - At least one first- or second-degree relative diagnosed with a BRCA-Related Cancer at age 40 or younger; or

- 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 carcinoma); or
- At least one first-degree relative with paraganglioma or pheochromocytoma; or
- At least one first-degree relative with a Cancer Associated with Lynch Syndrome; or
- At least one second-degree relative with a Cancer Associated with Lynch Syndrome diagnosed at age 50 or younger; or
- At least one second-degree relative with at least two Cancers Associated with Lynch Syndrome; or
- Two or more second-degree relatives with a Cancer Associated with Lynch Syndrome; or
- At least one first- or second-degree relative with a clinical diagnosis of familial adenomatous polyposis, attenuated familial adenomatous polyposis, juvenile polyposis syndrome or Peutz-Jeghers Syndrome; or
- 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.

Documentation Requirements

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The documentation requirements outlined below are used to assess whether the member meets the clinical criteria for coverage but do not guarantee coverage of the service requested.

CPT Codes*	Required Clinical Information
Genetic Testing for Hereditary Cancer	
0101U, 0102U, 0103U, 0129U, 0130U, 0131U, 0132U, 0133U, 0134U, 0135U, 0138U, 0238U, 81162, 81163, 81164, 81432, 81433, 81435, 81436, 81437, 81438, 81441	Medical notes documenting the following, when applicable: • Personal history of the condition, if applicable, including age at diagnosis • Complete family history (usually three-generation pedigree) relevant to condition being tested • Genetic testing results of family member, if applicable, and reason for testing • Ethnicity/ancestry (e.g., Ashkenazi Jewish), if reason for testing • Any prior genetic testing results • How clinical management will be impacted based on results of genetic testing • Genetic counseling (if available)

*For code descriptions, refer to the Applicable Codes section.

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, pancreatic cancer or metastatic or high-risk (Gleason Score > = 7) prostate cancer (National Comprehensive Cancer Network [NCCN], Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic 1.2023).

Breast Cancer: Either invasive carcinomas or non-invasive (in situ) ductal carcinoma types (NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic 1.2023).

Close Blood Relatives: Are defined as follows (NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic 1.2023):

- First-degree relatives include parents, siblings, and offspring
- Second-degree relatives include half-brothers/sisters, aunts/uncles, grandparents, grandchildren, and nieces/nephews affected on the same side of the family
- Third-degree relatives include first cousins, great-aunts/uncles, great-grandchildren, and great grandparents affected on same side of family

Founder Mutation: A Founder Mutation is a gene mutation observed with high frequency in a group that is or was geographically or culturally isolated, in which one or more of the ancestors was a carrier of the mutant gene. This phenomenon is often called a Founder effect (National Cancer Institute [NCI] Dictionary of Genetics; NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic 1.2023).

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).

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, and TP53 (NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic 1.2023).

Limited Family History: Defined as having fewer than two known first-degree or second-degree female relatives or 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 1.2023).

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 1.2022).

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).

Ovarian Cancer: Includes fallopian tube cancers and primary peritoneal carcinoma (NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic 1.2023).

Panel: A group of laboratory tests that are performed together to assess a body function or disease (Medicare, 2019; McGraw Hill, 2002).

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, 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 1.2023).

PREMM: 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.

Primary Solid Tumor: An abnormal mass of tissue, typically not containing any cysts or liquid component, that 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).

Triple-Negative Breast Cancer: Refers to any Breast Cancer that does not show expression of estrogen receptors (ER), progesterone receptors (PR) or human epidermal growth factor receptor 2 (HER2) (NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic 1.2023).

Applicable Codes

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

CPT Code	Description
BRCA1 and BRCA2	
0138U	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) mRNA sequence analysis (List separately in addition to code for primary procedure)
81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (i.e., detection of large gene rearrangements)
81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
Multi-Gene Panel	
0101U	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated (15 genes [sequencing and deletion/duplication], EPCAM and GREM1 [deletion/duplication only])
0102U	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated (17 genes [sequencing and deletion/duplication])
0103U	Hereditary ovarian cancer (e.g., hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated (24 genes [sequencing and deletion/duplication], EPCAM [deletion/duplication only])
0129U	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53)
0130U	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), targeted mRNA sequence analysis panel (APC, CDH1, CHEK2, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, and TP53) (List separately in addition to code for primary procedure)
0131U	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (13 genes) (List separately in addition to code for primary procedure)

CPT Code	Description
Multi-Gene Panel	
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
81441	Inherited bone marrow failure syndromes (IBMFS) (eg, Fanconi anemia, dyskeratosis congenita, Diamond-Blackfan anemia, Shwachman-Diamond syndrome, GATA2 deficiency syndrome, congenital amegakaryocytic thrombocytopenia) sequence analysis panel, must include sequencing of at least 30 genes, including BRCA2, BRIP1, DKC1, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, GATA1, GATA2, MPL, NHP2, NOP10, PALB2, RAD51C, RPL11, RPL35A, RPL5, RPS10, RPS19, RPS24, RPS26, RPS7, SBDS, TERT, and TINF2
81479	Unlisted molecular pathology procedure

Description of Services

Genetic testing for hereditary cancer susceptibility is used to predict an individual's risk of cancer development in the future. It has been estimated that 5-10% of all cancers are hereditary (Heald et al., 2016).

Hereditary Breast and Ovarian Cancer

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). The inherited tendency to develop Breast and Ovarian Cancer has been termed Hereditary Breast and Ovarian Cancer syndrome (HBOC). A markedly increased percentage of women found to have a harmful BRCA variant will develop Breast Cancer by the time they are 70-80 years old (55%-72% for BRCA1 and 45%-69% BRCA2), and 39%-44% of women with a harmful BRCA1 variant/11%-17% of women with a harmful BRCA2 variant will develop Ovarian Cancer by the time they reach 70-80 years of age. Other genes, such as CDH1, PALB2, PTEN, and TP53 have also been linked to a higher risk of HBOC. A deleterious mutation in one or more of these genes may be inherited from either parent, and later, an acquired mutation on the other allele can lead to cancer development.

Harmful BRCA1 and BRCA2 mutations also increase a woman's risk of developing a contralateral Breast Cancer and other cancers including fallopian tube cancer and primary peritoneal cancer. Men with harmful BRCA2 mutations (and to a lesser extent, BRCA1 mutations) also have an increased risk of Breast Cancer and prostate cancer. Any individual with harmful BRCA1 or BRCA2 variants is at an increased risk for pancreatic cancer, although the risk increase is lower (NCI, 2020).

Other Multi-Gene Hereditary Cancer Panels

Multi-Gene hereditary cancer Panels are available that include genes beyond those for specific cancer syndromes such as Lynch Syndrome (EPCAM, MLH1, MSH2, MSH6, PMS1, PMS2) or high-penetrance Breast Cancer susceptibility (including BRCA1, BRCA2, CDH1, PALB2, PTEN, and TP53). Many different test 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 1.2023; NCCN, Genetic/Familial High-Risk Assessment: Colorectal 1.2022; LaDuca et al., 2014; Robson et al., 2015; Kurian et al., 2014; Tung et al., 2015; Plon et al., 2011).

Clinical Evidence

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 1.2023).

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 Prediction of *MLH1* and *MSH2* Model (PREMM) (NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic 1.2023). 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 1.2023, NCCN, Genetic/Familial High-Risk Assessment: Colorectal 1.2022, NCCN, Prostate Cancer 4.2022)

Hereditary Cancer Type(s)	Commonly Associated Gene(s)
Hereditary breast and/or ovarian cancer	ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MSH2, MSH6, MLH1, PMS2, EPCAM, NF1, PALB2, PTEN, RAD51C, RAD51D, STK11, TP53
Colon cancer/polyposis	APC, ATM, AXIN2, BLM, BMPR1A, CHEK2, EPCAM, GALNT12, GREM1, MLH1, MSH2, MSH6, PMS2, MLH3, MSH3, MUTYH, NTHL1, PMS2, POLD1, POLE, PTEN, RNF43, RPS20, SMAD4, STK11, TP53
Pancreatic cancer	ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, STK11, TP53
Prostate cancer	BRCA1, BRCA2, PALB2

BRCA1/BRCA2

BRCA1 and BRCA2 genes are associated with causing HBOC. This syndrome results in an increased risk for breast cancer for men and women, and an increased risk for ovarian cancer in women. Other cancers have been associated with HBOC, particularly with BRCA2 variants, including prostate, pancreatic and melanoma. Management of HBOC for those with cancer includes bilateral mastectomy due to the high risk of breast cancer. Treatment of ovarian and other cancers is similar to sporadic cancers. Preventative measures for asymptomatic individuals include prophylactic bilateral mastectomy and oophorectomy, chemoprevention, and increased surveillance (Petrucelli et al., 2016).

Testing for BRCA1 and BRCA2 can include targeted variants for at risk populations, such as for those with Ashkenazi Jewish ancestry, full gene sequencing, and duplication/deletion analysis. BRCA1 accounts for about 66% of HBOC, and sequence analysis can identify variants in about 80% of cases for both BRCA1 and BRCA2. Duplication/deletion testing identifies variants in each gene in an additional 10% of cases (Petrucelli et al., 2016).

Several studies have shown that BRCA1 breast cancer is more likely to be characterized as triple negative. Studies have reported BRCA1 mutations in 7-28% of patients 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 1.2023). The triple-negative breast cancer phenotype, which carries an adverse prognosis, accounts for 80% to 90% of BRCA1-associated breast cancers. 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 ≤ 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 and Ovarian Cancer Multi-Gene Panels

Hayes (2021) 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 (PV/LPV) 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 pathogenic/likely pathogenic (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, 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 pathogenic and likely pathogenic 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 guidelines present evidence-based criteria for genetic testing for hereditary breast and/or ovarian cancer syndrome (NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic 1.2023). In these guidelines, the genetic testing recommendations go beyond BRCA1/BRCA2 and include other high-penetrance breast and/or ovarian cancer susceptibility genes including: CDH1, PALB2, PTEN, and TP53. The guidelines address genetic risk assessment, counseling, testing, and management based on test results. Additionally, the guidelines separate the testing into three categories: 1) clinically indicated; 2) may be considered; 3) low probability that testing will have clinical utility. In this third category the scenarios included are having no close blood relative with breast, ovarian, pancreatic, or prostate cancer and men with localized prostate cancer (Gleason score < 7) or women with Breast Cancer diagnosed at age > 65 years. The recommended NCCN criteria for testing include:

- Category: Clinically Indicated
  - A known BRCA1/BRCA2 mutation or other pathogenic/likely pathogenic mutation in a cancer susceptibility gene in the family
  - Persons who meet testing criteria but with limited previous testing and desire multi-gene testing
  - Known mutation identified on tumor genomic testing that has clinical implications if also identified in the germline
  - To aid in systemic therapy and surgical decision-making
  - Personal cancer history
    - Diagnosed with ovarian cancer
    - Diagnosed with exocrine pancreatic cancer
    - Diagnosed with male breast cancer
    - Diagnosed with prostate cancer at any age with one of the following:
      - Metastatic, intraductal/cribriform histology, or high- or very-high risk group
      - Any NCCN risk group with the following family history:
        - At least one close blood relative with breast cancer diagnosed age 50 or younger, triple negative breast cancer or male breast cancer at any age, or ovarian cancer, pancreatic cancer, or metastatic intraductal/cribriform histology or high- or very-high risk group prostate cancer at any age; or
        - At least two close blood relatives with Breast Cancer or prostate cancer diagnosed at any age
        - Ashkenazi Jewish ancestry
    - Diagnosed with breast cancer with one of the following conditions:
      - Diagnosed ≤ 50 years old
      - Diagnosed at any age with:
        - Multiple primary breast cancer (synchronous or metachronous) at any age
        - To aid in treatment decisions involving PARP inhibitors in the metastatic setting
        - To aid in adjuvant treatment decisions with Olaparib
        - Triple-negative breast cancer
        - Male breast cancer
        - Lobular breast cancer with personal or family history of diffuse gastric cancer
        - At least one close blood relative with breast cancer at age 50 or younger, ovarian, pancreatic, or metastatic, intraductal/cribriform histology or high- or very-high risk group prostate cancer at any age or male breast cancer at any age

        - An unknown or limited family history
        - Ashkenazi Jewish Ancestry
        - At least 3 total diagnoses of breast cancer in patient and/or close blood relatives
        - At least 2 close blood relatives with either breast or prostate cancer (any grade) at any age
    - Family history of cancer
        - Affected or unaffected individual has a first- or second-degree blood relative meeting above criteria (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making). *If the affected relative has pancreatic or prostate cancer, only first-degree relatives should be offered testing unless otherwise clinically indicated.
        - Affected or unaffected individual who does not meet other criteria but has a probability (> 5%) of a BRCA1/2 pathogenic variant based on probability models
- Category: May Be Considered
    - Unaffected individual of Ashkenazi Jewish descent without other risk factors

In addition, NCCN recommends that testing an individual in a family with a cancer diagnosis should first be discussed. If there are no living family members with breast or ovarian cancer available for testing, consider testing family members affected with other cancers associated with BRCA1/BRCA2, such as prostate cancer (Gleason Score ≥ 7 or metastatic), pancreatic cancer or melanoma. Due to potential difficulty in interpreting testing results in an unaffected person, testing of individuals without a cancer diagnosis should only be considered when there is no affected family member available for testing (NCCN, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic 1.2023).

National Society of Genetic Counselors (NSGC)

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. In addition to the recommended steps in the NSGC 2013 practice guideline for HBOC risk assessment (discussed below), NSGC recommends providing education focused on the basic principles of genetics and cancer and discussion of dissemination of information regarding testing performed and implications on testing of other family members.

The NSGC recommends that genetic testing be performed in the context of an informed decision-making process (Berliner et al., 2013). The process of cancer risk assessment and genetic counseling for HBOC syndrome requires many steps, including the following:

- Gathering personal medical and family history data
- Psychosocial assessment
- Discussion of cancer and mutation 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
- Review of issues related to genetic discrimination

Society of Gynecologic Oncology (SGO)

The SGO provided a statement on risk assessment and recommended that individuals with a likelihood of inherited predisposition to cancer based on personal or family history should be offered genetic counseling (Lancaster et al., 2015). Beyond this recommendation, there is additional guidance for criteria for patients with an increased likelihood of having an inherited predisposition to breast and ovarian/tubal/peritoneal cancer who should receive genetic counseling and be offered genetic testing including:
Women affected with:

- High grade epithelial ovarian/tubal/peritoneal cancer
- Breast cancer ≤ 45 years
- Breast cancer with close relative with breast cancer ≤ 50 years or close relative with epithelial ovarian/tubal/peritoneal cancer at any age

- Breast cancer ≤ 50 years with a limited family history
- Breast cancer with ≥ 2 close relatives with breast cancer at any age
- Breast cancer with ≥ 2 close relatives with pancreatic cancer, aggressive prostate cancer (Gleason score ≥ 7)
- Two breast primaries, with the first diagnosed prior to age 50
- Triple-negative breast cancer ≤ 60 years
- With breast cancer and Ashkenazi Jewish ancestry
- Pancreatic cancer with ≥ 2 close relatives with breast, ovarian/tubal/peritoneal, pancreatic, or aggressive prostate cancer (Gleason score ≥ 7)

Women unaffected with cancer, but with:
- A first-degree or several close relatives that meet one of the above criteria
- A close relative carrying a known BRCA1 or BRCA2 mutation
- A close relative with male breast cancer

In addition, the statement details criteria for patients with an increased likelihood of Lynch syndrome and for whom genetic assessment is recommended including:
- Patients with endometrial or colorectal cancer with evidence of microsatellite instability or loss of a DNA mismatch repair protein (MLH1, MSH2, MSH6, PMS2) on immunohistochemistry
- Patients with a first-degree relative affected with endometrial or colorectal cancer who was either diagnosed before age 60 years or who is identified to be at risk for Lynch syndrome by a systematic clinical screen that incorporates a focused personal and medical history
- Patients with a first or second-degree relative with a known mutation in a mismatch repair gene

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 a 2021 publication, Uson et al. reported that using universal multi-gene panel testing instead of practice guideline criteria-based testing in colorectal cancer (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 actional findings that would not have been detected with a CRC specific gene panel or if standard clinical practice criteria had been followed. Overall, 11% (1 in 10) had changes in their management based on test results. Family cascade testing was low (16%), which is a concerning observation and will require further study. Another concern was the demographic of the participants seen at the Mayo Clinic sites where the study was conducted, which may limit generalization of study results. Family history was self-reported, which may also limit accuracy and completeness, and the follow up was relatively short, impacting the utility of survival analysis to address outcomes fully. Lastly, the study was not able to track blood relatives that may have undergone cascade testing elsewhere. The researchers caution that further long-term follow up will be necessary to address outcomes on morbidity and cancer care decision-making.

Gupta et al. (2019) published insights regarding the NCCN updated guidelines for susceptibility screening for 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 ≥ 2.5% or MMRpro or MMRpredict score ≥ 5%
- Mismatch repair-deficient colorectal cancer, not attributed to MLH1 promoter methylation
- Individuals meeting any other genetic testing criteria
- ≥ 10 cumulative colorectal adenomas
- ≥ 3 cumulative gastrointestinal hamartomatous polyps

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

In 2022, 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
  - Tumor is dMMR: MSI-high or abnormal MMR IHC
  - Another LS-related cancer*
  - Family history of LS-related cancers in first or second-degree relatives
    - ≥ 1 relative(s) diagnosed at age < 50
    - ≥ 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
  - ≥ 1 first-degree relative(s) with > 1 diagnoses of LS-related cancers
  - ≥ 2 or more first-or second-degree relatives with LS-related cancers with ≥ 1 diagnosed age < 50
  - ≥ 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 1.2022). The guidelines address genetic risk assessment, counseling, testing, and management based on test results. The recommended NCCN criteria for genetic testing include:

- Possible Polyposis Syndromes:
  - ≥ 10 adenomas; or
  - ≥ 2 hamartomatous polyps; or
  - ≥ 5 serrated polyps/lesions proximal to the rectum
- Lynch Syndrome:
  - Known LS pathogenic variant in the family
  - Personal history of colorectal or endometrial cancer
    - Diagnosed at less than 50 years of age
    - Synchronous or metachronous LS cancer regardless of age
    - Family history of 1 first-degree or second-degree relative with an LS-related cancer diagnosed < 50
    - Two or more first-degree or second-degree relatives with an LS-related cancer regardless of age
  - Family history of Lynch syndrome associated cancers in close blood relatives of varying degrees
  - Individual with an increased model-predicted risk for Lynch syndrome associated cancers
  - Personal history of a tumor with a mismatch repair (MMR) deficiency or immunohistochemistry (IHC) diagnosed at any age

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 recommends that multi-gene testing is ideally offered with professional genetic expertise 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

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. 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.

A Hayes Precision Medicine Insight Report (2020) indicates there is minimal support in the evidence-based literature for use of multi-syndrome panel testing for aiding management of individuals who are suspected of having a hereditary cancer syndrome. Hayes found weak support both for and against use of multi-syndrome panel testing in professional guidelines and statements for those with suspected hereditary cancer syndromes. The report indicates that use of these panels depends primarily on patient population and states that available guidelines are lacking in specification regarding panel gene selection/composition.

LaDuca et al. (2020, included in Hayes 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 HIF2α EGLN1, and KIF1β as well as genes that are components of other hereditary tumor predisposition syndromes including RET, VHL, NF1, and FH. The authors notes that up to 35% of 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, included in Hayes 2020). 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 significant 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 can't 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.

Parsons et al. (2016) conducted a study to determine the prevalence of somatic and germline mutations in children with solid tumors. From August 2012 through June 2014, children with newly diagnosed and previously untreated central nervous system (CNS) and non-CNS solid tumors were prospectively enrolled in the study at a large academic children's hospital. Blood and tumor samples underwent whole exome sequencing (WES) in a certified clinical laboratory with genetic results categorized by clinical relevance. A total of 150 children participated, with a mean age of 7 years, with 80 boys and 70 girls. Tumor samples were available for WES in 121 patients. In this group, somatic mutations with established clinical utility were found in 4 patients,

and mutations with possible clinical utility were found in 29. CTNNB1 had the most mutations, followed by KIT, TSC2, BRAF, KRAS, and NRAS. Diagnostic germline mutations related to the child's clinical presentation was found in 150 patients and included 13 dominant mutations in known cancer susceptibility genes, including TP53, VHL, and BRCA1. One recessive liver disorder with liver cancer was identified in TJP2 and one renal cancer, CLCN5. Incidental findings were found in 8 patients. Nearly all patients (98%) had variants of unknown significance in known cancer genes, drug response genes, and genes known to be associated with recessive disorders.

Lincoln et al. (2015) tested 1105 individuals using a 29-gene NGS panel. The 1105 cases included 1062 clinical cases (735 patients prospectively accrued following NCCN guidelines for HBOC, 118 patients with known familial mutations, 209 patients retrospectively collected with high-risk criteria). Of the 1062 clinical cases, 975 had previously received BRCA1/2 testing and the results showed a concordance of 99.8%. Overall, 260 variants were determined. The 735 prospective patients had 66 patients (9.0%) with a BRCA1 or BRCA2 variant. Twenty-six patients (3.9%) were BRCA-negative but had variants in other genes with known associated to breast/ovarian cancer or those associated with Lynch syndrome. Most common non-BRCA findings were ATM (five cases), PALB2 (five cases), CHEK2 (three cases), and the Lynch syndrome genes (eight cases). Another 2.7% of these BRCA-negative patients were carriers of MUTYH. The high-risk patients (n = 2009) were determined to have BRCA1 or BRCA2 in 40% of the patients and of the BRCA-negative individuals, 6.1% were positive of another variant. The researchers found that variants of uncertain significance (VUS) increased as the number of genes was tested. Of the 1062 clinical cases, 41.0% had at least one VUS and of those 11.4% had two or more. Additionally, 68% of the VUS detected were rare, missense variants that were not identified in the 1000Genomes Project. They concluded that NGS testing of panels can offer results that may be missed by traditional testing, but the issue with understanding and addressing VUS remains a challenge.

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).

Endocrine Society

An algorithm for genetic testing when a PGL-PCC syndrome is suspected was developed by the Endocrine Society task force, comprised of members from the Endocrine Society, European Society of Endocrinology, and American Association for Clinical Chemistry (Lenders et al., 2014). Identifying which gene is responsible for a suspected PGL-PCC syndrome can aid in determining a therapeutic approach. When a PCC or PGL is present, the patient's family and medical history should be examined for known syndrome of NF1, MEN II and VHL, and if appropriate, targeted genetic testing should take place. In the presence of metastatic disease, the succinate dehydrogenase subunit genes should be evaluated. In non-metastatic disease, and the absence of a clear syndrome, genetic testing should be targeted on the basis of other laboratory results for adrenal and extra-adrenal adrenergic results:

- Extra-adrenal:
  - Dopaminergic-SDHB, SDHD, SDHC
  - Noradrenergic- SDHB, SDHD, SDHC, VHL, MAX
- Adrenal:
  - Dopaminergic-SDHB, SDHD, SDHC
  - Noradrenergic- VHL, if negative, SDHB, SDHD, SDHC, MAX
  - Adrenergic-RET, if negative, TMEM127, MAX

NCCN

NCCN Practice Guidelines for Prostate Cancer (4.2022) indicate that germline testing is recommended for individuals with a personal history of prostate cancer in the following scenarios:

- Metastatic, regional (node positive), very-high risk localized, high-risk localized prostate cancer
- Family history including at least one of the following:
  - ≥ 1 first-, second-, or third-degree relative with:
    - breast, colorectal or endometrial cancer at ≤ 50 years of age
    - male breast cancer, ovarian, exocrine pancreatic or metastatic, regional, very-high-risk, high-risk prostate cancer at any age
  - ≥ 1 first-degree relative (father or brother) with prostate cancer at ≤ 60 years of age
  - ≥ 2 first-, second-, or third-degree relatives with breast or prostate cancer at any age
  - ≥ 3 first- or second-degree relatives with Lynch syndrome-related cancers, especially if diagnosed < 50 y: colorectal, endometrial, gastric, ovarian, exocrine pancreas, upper tract urothelial, glioblastoma, biliary tract, and small intestinal cancer
  - A known family history of familial cancer risk mutation (pathogenic/likely pathogenic variants), especially in: BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6, PMS2, EPCAM
  - Ashkenazi Jewish ancestry
- Personal history of breast cancer

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

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

NCCN Clinical Practice Guidelines for Pancreatic Adenocarcinoma (1.2022) 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.

NCCN Clinical Practice Guidelines for Neuroendocrine and Adrenal Tumors (1.2022) state the following:
Growing evidence shows 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. Genetic counseling, with genetic testing when appropriate, is recommended in patients with a pheochromocytoma or paraganglioma since a significant 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 11, 2022)

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Policy History/Revision Information

Date	Summary of Changes
10/01/2023	**Application** ***Individual Exchange Plans*** • Removed language indicating this Medical Policy does not apply to Individual Exchange benefit plans in the states of Massachusetts, Nevada, and New York **Supporting Information** • Archived previous policy version 2023T0009LL

Instructions for Use

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

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

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