

GENETIC TESTING FOR HEREDITARY CANCER

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[Instructions for Use](#) ⓘ

Table of Contents	Page
COVERAGE RATIONALE	1
DOCUMENTATION REQUIREMENTS	3
DEFINITIONS	4
APPLICABLE CODES	4
DESCRIPTION OF SERVICES	6
CLINICAL EVIDENCE	6
U.S. FOOD AND DRUG ADMINISTRATION	15
REFERENCES	15
GUIDELINE HISTORY/REVISION INFORMATION	20
INSTRUCTIONS FOR USE	20

Related Medical Management Guideline
• Preventive Care Services

COVERAGE RATIONALE

Genetic counseling is strongly recommended prior to these tests in order to inform persons being tested about the advantages and limitations of the test as applied to a unique person.

Hereditary Breast and Ovarian Cancer (BRCA1/BRCA2)

Genetic testing for BRCA1 and BRCA2 for individuals with a personal history of a related cancer is proven and medically necessary in the following situations:

- Men with a personal history of Breast Cancer.
- Women with a personal history of Ovarian Cancer.
- Women with a personal history of Breast Cancer in any of the following situations:
 - Metastatic Breast Cancer and may be a candidate for treatment with a PARP inhibitor (e.g., olaparib).
 - Breast Cancer diagnosed at any age in an individual with at least one close (1st-, 2nd-, and 3rd-degree relative) blood relative who has a BRCA1 or BRCA2 mutation
 - Breast Cancer diagnosed at any age in an individual with Ashkenazi Jewish ancestry.
 - Breast Cancer diagnosed at any age with any one of the following:
 - At least one Close Blood Relative with Ovarian Cancer; or
 - At least one close male blood relative with Breast Cancer; or
 - At least one Close Blood Relative with Breast Cancer diagnosed at age 50 or younger; or
 - At least one Close Blood Relatives with pancreatic cancer
 - At least one Close Blood Relative with metastatic prostate cancer at any age; or
 - At least two Close Blood Relatives with Breast Cancer, pancreatic cancer, and/or prostate cancer at any age; or
 - An unknown or Limited Family History (see [Definitions](#) section for further clarification of Limited Family History).
 - Breast Cancer diagnosed at age 45 or younger
 - "Triple-Negative" (Her2 negative, ER negative and PR negative) Breast Cancer diagnosed at age 60 or younger;
 - Breast Cancer diagnosed at age 50 or younger with any of the following:
 - An additional Breast Cancer primary (prior diagnosis or bilateral cancer); **or**
 - At least one Close Blood Relative with Breast Cancer or pancreatic cancer or prostate cancer; **or**
 - An unknown or Limited Family History (see [Definitions](#) section for further clarification of Limited Family History).
- Individuals with a personal history of pancreatic cancer.
- Men with a personal history of prostate cancer in any of the following situations:
 - At least one Close Blood Relative who has a BRCA1 or BRCA2 mutations.
 - Metastatic prostate cancer diagnosed at any age.
 - High Risk prostate cancer (Gleason Score at least 7) diagnosed at any age with any of the following:
 - At least one Close Blood Relative with Ovarian Cancer or

- At least one Close Blood Relative with Breast Cancer diagnosed at age 50 or younger; or
 - At least one Close Blood Relative with pancreatic cancer at any age; or
 - At least one Close Blood Relative with metastatic prostate cancer at any age; or
 - At least two Close Blood Relatives with Breast Cancer, pancreatic cancer and/or prostate cancer; or
 - An unknown or Limited Family History.
- Individuals with a *BRCA 1/2* pathogenic mutation detected in tumor tissue.

Genetic testing for *BRCA1* and *BRCA2* for individuals *without* a personal history of a related cancer is proven and medically necessary in the following situations:

- When there is a known *BRCA1/BRCA2* mutation in a Close Blood Relative (defined as first-, second- or third-degree relative)
- When there is at least one of the following familial risk factors:
 - At least one first- or second-degree blood relative meeting any of the above criteria for individuals with a personal history of a related cancer; or
 - At least one third-degree blood relative with Breast Cancer and/or Ovarian Cancer who has at least two Close Blood Relatives with Breast Cancer (at least one with Breast Cancer at age 50 or younger) and/or Ovarian Cancer.

Genetic testing for *BRCA1* and/or *BRCA2* testing is unproven and not medically necessary for all other indications including:

- Screening for Breast or Ovarian 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

Further evidence is needed to establish the clinical utility of testing in other populations.

Multi-Gene Hereditary Cancer Panel Testing Criteria:

Genetic testing with a multi-gene hereditary cancer panel in individuals with an indication for testing for hereditary Breast and Ovarian Cancer is proven and medically necessary if all of the following criteria are met:

- The suspected hereditary cancer syndromes can be diagnosed by testing of one or more genes included in the specific hereditary cancer panel; and
- The results of testing will directly impact this patient's medical management; and
- The individual meets at least one of the criteria in Hereditary Breast and Ovarian Cancer (*BRCA1/BRCA2*) (see above section); and
- The individual has a family history or personal history that is strongly suggestive of **more than one** hereditary cancer syndrome including at least one of the following:
 - A personal history of at least two different cancers (e.g. Breast Cancer and Ovarian Cancer)
 - A personal history of cancer diagnosed at age 40 or younger.
 - A personal history of cancer and at least one relative with a cancer associated with Lynch Syndrome (i.e. brain, colorectal, endometrial, gastric, ovarian, pancreatic, renal pelvis, small intestine, or ureter cancers, sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas).
 - At least one Close Blood Relative diagnosed with Breast Cancer, Ovarian Cancer, prostate cancer or pancreatic cancer at age 40 or younger
 - At least three Close Blood Relatives on the same side of the family diagnosed with any cancer

Genetic testing with a multi-gene cancer panel in individuals with an indication for testing for hereditary colorectal cancer is proven and medically necessary in the following situations:

- The suspected hereditary cancer syndromes can be diagnosed by testing of one or more genes included in the specific hereditary cancer panel; and
- The results of testing will directly impact this individual's medical management; and
- The individual has a personal or family history with at least one of the following criteria for Hereditary Colorectal Cancer/Lynch Syndrome Cancer or colorectal polyposis syndrome:
 - Men with a personal history of colorectal cancer or women with a personal history of colorectal or endometrial cancer diagnosed at age 50 or younger.
 - Men with a personal history of colorectal cancer or women with a personal history of colorectal or endometrial cancer diagnosed at age 51 or later with at least one of the following criteria:
 - A personal history of another cancer associated with Lynch Syndrome (i.e. brain, gastric, ovarian, pancreatic, renal pelvis, small intestine, or ureter cancers, sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas); or
 - Tumor testing results showing that their colorectal or endometrial cancer was MSI-high or had immunohistochemical (IHC) staining showing the absence of one or more mismatch repair proteins (*MLH1, MSH2, MSH6 or PMS2*).

- A personal history of colorectal polyposis with at least 10 adenomatous polyps, at least 2 hamartomatous polyps, or at least 5 serrated polyps.
- At least one Close Blood Relative with a diagnosis of colorectal cancer or endometrial cancer at age 50 or younger.
- At least one Close Blood Relative with at least two cancers associated with Lynch Syndrome (i.e. brain, colorectal, endometrial, gastric, ovarian, pancreatic, renal pelvis, small intestine, or ureter cancers, sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas).
- Two or more Close Blood Relatives with a cancer associated with Lynch Syndrome (i.e. brain, colorectal, endometrial, gastric, ovarian, pancreatic, renal pelvis, small intestine, or ureter cancers, sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas), with at least one diagnosed at age 50 or younger.
- Three or more Close Blood Relatives with a cancer associated with Lynch Syndrome (i.e. brain, colorectal, endometrial, gastric, ovarian, pancreatic, renal pelvis, small intestine, or ureter cancers, sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas) diagnosed at any age.
- At least one Close Blood Relative with a clinical diagnosis of Familial Adenomatous Polyposis, Attenuated Familial Adenomatous Polyposis, Juvenile Polyposis Syndrome, or Peutz-Jeghers Syndrome.
- A PREMM5, PREMM1,2,6, MMRpro, or MMRpredict Score of 5% or greater for having a Lynch syndrome gene mutation.

Genetic testing with a multi-gene hereditary cancer panel in individuals without an indication for testing for hereditary Breast and Ovarian Cancer or colorectal cancer is proven and medically necessary in the following situations:

- The suspected hereditary cancer syndromes can be diagnosed by testing of one or more genes included in the specific hereditary cancer panel; and
- The results of testing will directly impact this individual’s medical management; and
- The individual has a family history or personal history that is strongly suggestive of **more than one** hereditary cancer syndrome.

Genetic testing with a multi-gene hereditary cancer panel in individuals diagnosed with cancer at age 18 or younger is proven and medically necessary.

Genetic testing with a multi-gene cancer panel is proven and medically necessary in an individual who has previously tested negative (indeterminate) for the high Penetrance genes that are most likely to explain the personal or family history of cancer (e.g., BRCA1/2 for Breast Cancer and Ovarian Cancer) in the following situations:

- The suspected hereditary cancer syndromes can be diagnosed by testing of one or more genes included in the specific hereditary cancer panel; and
- The results of testing will directly impact this individual’s medical management; and
- The individual’s personal and family history remains strongly suggestive of an inherited susceptibility that can be diagnosed by testing of one or more genes included in the specific hereditary cancer panel including at least one of the following:
 - A personal history of at least two different cancers (e.g. Breast Cancer and Ovarian Cancer).
 - A personal history of cancer diagnosed at age 40 or younger.
 - A personal history of cancer and at least one relative with a cancer associated with Lynch Syndrome (i.e. brain, colorectal, endometrial, gastric, ovarian, pancreatic, renal pelvis, small intestine, or ureter cancers, sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas).
 - At least one Close Blood Relative diagnosed with Breast Cancer, Ovarian Cancer, prostate cancer or pancreatic cancer at age 40 or younger.
 - At least three Close Blood Relatives on the same side of the family diagnosed with any cancer.

Multi-gene hereditary cancer panels are unproven and not medically necessary for all other 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.

Required Clinical Information

Genetic Testing for Hereditary Cancer

Medical notes documenting **all** of the following:

- 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

Genetic Testing for Hereditary Cancer

- 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)

DEFINITIONS

Please note, for the purpose of this policy:

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.

Breast Cancer: Either invasive carcinomas or non-invasive (in situ) ductal carcinoma types (NCCN 2018a).

Close Blood Relatives: Are defined as follows (NCCN 2017):

- 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 website) (NCCN 2017).

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, 2018b).

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 2017).

Lynch Syndrome Cancers: colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal pelvis, brain (usually glioblastoma), small intestinal cancers, sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas as seen in Muir-Torre syndrome (NCCN, 2017b).

Ovarian Cancer: includes fallopian tube cancers and primary peritoneal carcinoma (NCCN, 2018).

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, 2017b).

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.

Triple-Negative Breast Cancer: refers to any Breast Cancer that does not show expression of estrogen receptors (ER), progesterone receptors (PR) or HER2/neu (NCCN, 2017a).

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 guideline 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 CPT codes	
81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (i.e., detection of large gene rearrangements)
81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
81165	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81166	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
81167	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
81212	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
81215	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
81216	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81217	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
Multi-Gene Panel CPT Codes	
0101U	Hereditary colon cancer disorders (e.g., Lynch syndrome, <i>PTEN</i> 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], <i>EPCAM</i> and <i>GREM1</i> [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], <i>EPCAM</i> [deletion/duplication only])
0104U	Hereditary pan cancer (e.g., hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal 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 (32 genes [sequencing and deletion/duplication], <i>EPCAM</i> and <i>GREM1</i> [deletion/duplication only])
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

CPT Code	Description
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

CPT Code	Description
Multi-Gene Panel CPT Codes	
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

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 (BRCA1/BRCA2)

Breast Cancer is the second most common cause of cancer-related deaths among women. The inherited tendency to develop Breast and Ovarian Cancer has been termed the hereditary Breast and Ovarian Cancer syndrome (HBOC). Mutation in either of two genes, *BRCA1* and *BRCA2*, has been associated with an increased risk for Breast and Ovarian Cancer. A deleterious mutation in either gene may be inherited from either parent; and later an acquired mutation of the other allele can lead to cancer development.

It has been estimated that inherited *BRCA1* and *BRCA2* mutations account for 5 to 10 percent of Breast Cancers and 10 to 15 percent of Ovarian Cancers among white women in the United States (National Cancer Institute [NCI], 2015). Harmful *BRCA1* mutation may also increase a woman's risk of developing other cancers. Men with a harmful *BRCA1* mutation also have an increased risk of Breast Cancer and, possibly, of pancreatic cancer, testicular cancer, and early-onset prostate cancer. However, male Breast Cancer, pancreatic cancer, and prostate cancer appear to be more strongly associated with *BRCA2* gene mutation (Thompson and Eaton, 2002; NCCN, 2017).

Multi-Gene Hereditary Cancer Panels

Multi-gene hereditary cancer panels using next generation sequencing technology are currently available, and 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 a patient'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 2017; NCCN 2018b; 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, 2017a). A small subset of these inherited cancers, about 15-20%, may be the result of a complex interaction between multiple genes (ASCO 2018).

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 that 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 syndrome. When applicable, risk assessment tools should be utilized to help identify the risk an individual has a hereditary cancer gene (NCCN 2017). Some examples of tools include BRCAPRO, the Breast and Ovarian Cancer Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) (NCCN 2017) and Prediction of MLH1 and MSH2 Model (PREMM) (NCCN 2018b). Genetic testing is recommended generally 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).

Table 1 lists common cancers that can be hereditary, the associated genes, and references that can be utilized to learn about each hereditary cancer syndrome in more detail.

Hereditary Cancer Syndrome(s)	Gene(s)	Associated Cancer(s) and References
Hereditary Breast and Ovarian Cancer	<i>BRCA1, BRCA2, CHEK2, PALB2, BRIP1, RAD51C, RAD51D¹, PTEN, TP53, STK11, NBN, ATM, CDH1</i>	<ul style="list-style-type: none"> Breast (Antoniou et al. 2003; Chen et al. 2006; Hilgart et al 2012; Shiovitz 2015, Daly et al. 2017) Ovarian (Risch et al. 2001; Chen et al. 2006; Lancaster et al 2015) Fallopian tube (Medeiros et al. 2006; Lancaster et al 2015) Primary peritoneal (Casey et al. 2005; Finch et al. 2012; Lancaster et al 2015) Pancreatic (BCLC, 1999; van Asperen et al. 2005; Mersch et al 2015) Prostate (Risch et al. 2001; Thompson et al. 2002; van Asperen et al. 2005; Mersch et al 2015) Melanoma (BCLC, 1999; Mersch et al 2015) Gastric/stomach (BCLC, 1999)
Familial adenomatous polyposis (FAP)	<i>APC</i>	<ul style="list-style-type: none"> Breast (He et al. 2016) Ovarian (Mostowska et al. 2014) Colorectal (Feng et al. 2014; Slowik et al. 2015; Leshno et al. 2016) Pancreatic (Leshno et al. 2016) Skin (Leshno et al. 2016) Thyroid (Septer et al. 2013)
Ataxia-telangiectasia	<i>ATM</i>	<ul style="list-style-type: none"> Breast (Marabelli et al. 2016) Sarcoma (Ballinger et al. 2016) Lung (Bhowmik et al. 2015; Huang et al. 2016) Gastric (Helgason et al. 2015) Melanoma (Antonopoulou et al. 2015) Pancreatic (Roberts et al. 2016)
PTEN hamartoma tumor syndrome/Cowden syndrome	<i>PTEN</i>	<ul style="list-style-type: none"> Breast (Slattery et al. 2012; Ozturk et al. 2013) Endometrial (Eng, 2016) Gastric/digestive (Gao et al. 2013) Colorectal (Jing et al. 2014) Thyroid (Eng, 2016)
Hereditary nonpolyposis colon cancer (HNPCC)/Lynch syndrome	<i>EPCAM, MLH1, MSH2, MSH6, PMS1, PMS2</i>	<ul style="list-style-type: none"> Breast (Smolarz et al. 2015; Kappil et al. 2016; Stoffel et al. 2015; Boland, 2018) Ovarian (Watson et al. 2008; Bonadona et al. 2011; Auranen, 2011) Colorectal (Senter et al. 2008; Raskin et al. 2011) Hepatocellular (Kohlmann and Gruber, 2014) Endometrial/uterine (Raskin et al. 2011; Castellsagué et al. 2015; Watson et al. 2008; Renkonen-Sinisalo, 2007; Auranen, 2011)

Hereditary Cancer Syndrome(s)	Gene(s)	Associated Cancer(s) and References
Peutz-Jeghers syndrome	<i>STK11 (LKB1)</i>	<ul style="list-style-type: none"> Breast (Boardman et al. 1998) Ovarian (McGarrity et al. 2016) Colorectal (Slattery et al. 2010) Gastric (Giardiello et al. 1987) Pancreatic (Klein et al. 2001)
Li-Fraumeni syndrome	<i>TP53</i>	<ul style="list-style-type: none"> Breast (Sagne et al. 2013; Mai et al. 2016) Ovarian (Schildkraut et al. 2010) Brain/CNS (Mai et al. 2016) Prostate (Borges and Ayres, 2015) Sarcoma (Mai et al. 2016) Thyroid (Chen et al. 2015)
Hereditary diffuse gastric cancer syndrome	<i>CDH1</i>	<ul style="list-style-type: none"> Breast (Benusiglio et al. 2013; Hansford et al. 2015) Gastric (Hansford et al. 2015)
Juvenile polyposis syndrome	<i>BMPR1A, SMAD4</i>	<ul style="list-style-type: none"> Gupta et al. (2017)
Hereditary mixed polyposis	<i>POLD1, GREM1, POLE</i>	<ul style="list-style-type: none"> Gupta et al. (2017)

BRCA1/BRCA2

The *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 includes prophylactic bilateral mastectomy and oophorectomy, chemoprevention, and increased surveillance (Petrucci 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 (Petrucci et al. 2016).

The National Comprehensive Cancer Network (NCCN) guidelines present evidence based specific criteria for genetic testing for hereditary breast and/or Ovarian Cancer syndrome caused by *BRCA1/BRCA2*. The guidelines address genetic risk assessment, counseling, testing and management based on test results (NCCN 2018b). The recommended NCCN criteria for testing include:

- Those diagnosed with Ovarian Cancer
- A known *BRCA1/BRCA2* mutation in the family
- Breast Cancer diagnosed **at** age 46-50 with:
 - An additional breast primary
 - A Close Blood Relative with high-grade (Gleaso Score > 7) prostate cancer
 - An unknown or limited family history
- Triple negative Breast Cancer diagnosed ≤ age 60
- Two Breast Cancer primaries in an individual
- Breast Cancer at any age with:
 - At least one Close Blood Relative with Breast Cancer diagnosed age 50 or younger, or Ovarian Cancer or male Breast Cancer, or pancreatic cancer, or metastatic prostate cancer
 - At least two Close Blood Relatives with Breast Cancer diagnosed at any age
 - Ashkenazi Jewish Ancestry
- Diagnosed with male Breast Cancer
- Diagnosed with metastatic prostate cancer
- Diagnosed with high-grade prostate cancer (Gleason Score>7) with:
 - At least one close blood relative with Breast Cancer diagnosed age 50 or younger, or Ovarian Cancer, or pancreatic cancer, or metastatic prostate cancer
 - At least two Close Blood Relatives with Breast Cancer or prostate cancer diagnosed at any age
 - Ashkenazi Jewish ancestry
- *BRCA1/2* pathogenic or likely pathogenic variant detected by tumor profiling

In addition, (NCCN recommends testing an individual in a family with a cancer diagnosis first should 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 difficulting 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, 2017a).

The U.S. Preventive Services Task Force (Moyer, 2014) recommends that primary care providers screen women who have family members with breast, ovarian, tubal or peritoneal cancer 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 include the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, and FHS-7. Women with positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing (Grade B). Screening should occur at age 18, and every 5-10 years after that to assess for family history changes. In addition, the USPSTF recommends against routine genetic counseling or BRCA testing for women whose family history is not associated with an increased risk for potentially harmful mutations in the *BRCA1* or *BRCA2* genes (Grade D).

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 a 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. Overtime the disparities between the two groups was 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 test 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.

Of 211 Ashkenazi Jewish Breast Cancer probands with a family history of pancreatic cancer, Stadler et al. (2011) 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.

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%).

Several studies have shown that *BRCA1* Breast Cancer is more likely to be characterized as triple-negative. Studies have reported *BRCA1* mutations in 9-28% 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 2017).

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) (National Cancer Institute 2018a; 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.

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.

The prevalence of *BRCA1/2* LRs was investigated in 48,456 patients with diverse clinical histories and ancestries that were referred for clinical molecular testing for suspicion of hereditary breast and Ovarian Cancer. 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, large rearrangement (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).

A study (Walsh 2006) found that the only genetic test commercially available in the United States to determine risk for development of hereditary Breast Cancer failed to detect *BRCA1* and *BRCA2* mutations in approximately 12% of Breast Cancer patients (n=300) who were members of a family with at least four cases of Breast Cancer and/or Ovarian Cancer. In this study, researchers retested participants for carrier status of genetic mutations known to influence risk for development of Breast Cancer using a molecular method not currently cleared for market in the United States known as multiplex ligation-dependent probe amplification (MLPA). Prior to enrollment, all participants had received a negative result from the Breast Cancer genetic test (Myriad Genetics Inc.) used routinely in the United States. The results of MLPA analysis indicated that 17% of study participants were, in fact, carriers of Breast Cancer-relevant genetic mutation, with 12% found to have alterations of *BRCA1* or *BRCA2*. Inherited alterations of *BRCA1* were more frequent among participants who were diagnosed with Breast Cancer prior to 40 years of age (16%) than among those who were older when diagnosed (6.5%). The clinical implications of these findings cannot be generalized to other populations, but results strongly suggest that improved methods for determining Breast Cancer risk are needed for individuals with strong family histories of breast and/or Ovarian Cancer.

Unger et al. (2000) assessed the frequency of genomic rearrangements in *BRCA1* was in 42 American families with breast and Ovarian Cancer who were seeking genetic testing and who were subsequently found to be negative for *BRCA1* and *BRCA2* coding-region mutations. The exon 13 duplication was detected in one family, and four families had other genomic rearrangements. A total of 5 (11.9%) of the 42 families with breast/Ovarian Cancer who did not have *BRCA1* and *BRCA2* coding-region mutations had mutations in *BRCA1* that were missed by conformation-sensitive gel electrophoresis or sequencing. Four of five families with *BRCA1* genomic rearrangements included at least one individual with both breast and Ovarian Cancer; therefore, four (30.8%) of 13 families with a case of multiple primary breast and Ovarian Cancer had a genomic rearrangement in *BRCA1*. Families with genomic rearrangements had prior probabilities of having a *BRCA1* mutation, ranging from 33% to 97% (mean 70%). In contrast, in families without rearrangements, prior probabilities of having a *BRCA1* mutation ranged from 7% to 92% (mean 37%).

Professional Societies

American College of Obstetricians and Gynecologists (ACOG)

In a 2009 practice bulletin (reaffirmed 2015), the ACOG recommended criteria for genetic risk assessment of hereditary breast and Ovarian Cancer syndrome (HBOC). These recommendations conclude:

- BRCA positive women should be offered salpingo-oophorectomy by age 40 or when childbearing is completed.
- For a risk reducing bilateral salpingo-oophorectomy, all tissue from the ovaries and fallopian tubes should be removed. Thorough visualization of the peritoneal surfaces with pelvic washings should be performed. Complete, serial sectioning of the ovaries and fallopian tubes is necessary, with microscopic examination for occult cancer.
- Genetic risk assessment is recommended for patients with a greater than an approximate 20-25% chance of having an inherited predisposition to Breast Cancer and Ovarian Cancer. This includes women with the following:
 - A close relative (mother, sister, daughter, grandmother, granddaughter, aunt or niece) with a known BRCA mutation
 - Personal history of both breast and Ovarian Cancer
 - Ovarian Cancer and a close relative with Ovarian Cancer or premenopausal Breast Cancer or both
 - Ovarian Cancer and Ashkenazi Jewish ancestry
 - Breast Cancer by age 40 years and Ashkenazi Jewish ancestry
 - Breast Cancer by age 50 years and a close relative with Ovarian Cancer or male Breast Cancer

Additionally, in a 2017 Committee Opinion (ACOG 2017), 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 Clinical Oncology (ASCO)

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 Society of Genetic Counselors (NSGC)

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 hereditary breast and Ovarian Cancer 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

Multi-Gene Hereditary Cancer Panels

Multi-gene hereditary cancer panels can be used to investigate various cancers through the use of evaluating multiple genes simultaneously. In some situations, the use of a multi-gene panel test may result in a cost and time efficient approach. This is most useful where multiple high-penetrance genes with actionable results are possible because it is difficult to predict which gene is most likely to be mutated based on personal or family medical history (Robson et al. 2015).

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.

Daly et al. (2017) provided an overview to NCCN breast and ovarian cancer susceptibility screening guideline updates, and Gupta et al. (2017) published insights regarding the NCCN 2017 updated for susceptibility screening for colorectal cancer syndromes, specifically around multigene cancer panels. They commented that multigene testing should focus on clinically actionable genes, and avoid the inclusion of low to moderate risk genes that lack evidence regarding risk management strategies. After review of available evidence, Daly et al. (2017) identified the known high and moderate penetrance genes with available guidelines or recommendations on risk surveillance and/or management, which included for breast and ovarian cancer, *BRCA1/2*, *TP53*, and *PTEN* (high penetrance) and *ATM*, *BRIP1*, *CDH1*, *CHEK2*, *NBN*, *PALB2*, *RAD51C*, *RAD51D*, and *STK11* (moderate penetrance). Gupta et al. (2017) noted that high or moderate penetrance genes with published guidelines or recommendations for risk management/surveillance included *APC*, *BMPRI1A*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *PMS2*, *PTEN*, *SMAD4*, *STK11*, *TP53*, *POLD1*, *GREM1*, and *POLE*. Both authors noted that these lists are not an endorsement by NCCN of specific genes or panels, but was provided for educational purposes to aid clinicians in selecting an appropriate panel for their patients.

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.

An analysis of 252,223 individuals by a 25-gene pan-cancer panel was performed by Rosenthal et al. (2017). Of these individuals, the majority (92.8%) met testing criteria for Hereditary Breast and Ovarian Cancer (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.

Lincoln et al. (2015) tested 1105 individuals using a 29-gene next-generation sequencing 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.

Zhang et al. (2015) studied the prevalence of cancer pre-disposition germline mutations in children and adolescents with cancer in 1,120 patients under the age of 20. Whole exomes were sequenced in 456 patients and whole genomes were sequenced in 595, or both in 69. Results were analyzed in 565 genes, including 60 that are associated with autosomal dominant cancer syndromes. Genetic variant pathogenicity was determined by a team of experts who relied on peer reviewed literature, cancer and locus specific databases, computational predictions, and second hits identified in the participant tumor genome. This same variant calling approach was used to analyze data on 966 controls from the 1000 Genomes Projects who were not known to have cancer, and data from 733 children from an autism study. Overall, germline mutations were found in 95 children with cancer (8.5%), as compared to only 1.1% of 1000 Genome Project and 0.6% of autism study controls. The mutations were most commonly found in *TP53*, *APC*, *BRCA2*, *NF1*, *PMS2*, *RB1* and *RUNX3*. Eighteen patients also have variants in tumor suppressor genes. Of the 58 patients who had family history information available and a mutation in a predisposing dominant cancer gene, 40% had a significant family history of cancer.

Parsons et al. 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 patient (98%) had variants of unknown significance in known cancer genes, drug response genes, and genes known to be associated with recessive disorders.

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, HIP2A 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.

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.

Pilie et al (2017) used a multigene 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 multigene 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 next generation sequencing 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 used. 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 multigene 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 multigene 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 multigene hereditary cancer panel testing.

Professional Societies

American Society of Clinical Oncology (ASCO)

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 multigene 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

American College of Gastroenterology (ACG)

The ACG published recommendations for the management of patients with hereditary gastrointestinal cancer syndromes, including genetic testing recommendations, in 2015 (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 multigene panels and next generation sequencing technology, noting that genetic specialists are increasingly using next-generation sequencing 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.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

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>.

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GUIDELINE HISTORY/REVISION INFORMATION

Date	Action/Description
07/01/2019	<p>Template Update</p> <ul style="list-style-type: none">Added <i>Documentation Requirements</i> section <p>Applicable Codes</p> <ul style="list-style-type: none">Updated list of applicable CPT codes for multi-gene panel to reflect quarterly code edits; added 0101U, 0102U, 0103U, and 0104U <p>Supporting Information</p> <ul style="list-style-type: none">Archived previous policy version MMG050.J

INSTRUCTIONS FOR USE

This Medical Management Guideline 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 benefit plan. In the event of a conflict, the member specific benefit plan document governs. Before using this guideline, 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 Management Guideline is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare West Medical Management Guidelines 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.

Member benefit coverage and limitations may vary based on the member's benefit plan Health Plan coverage provided by or through UnitedHealthcare of California, UnitedHealthcare Benefits Plan of California, UnitedHealthcare of Oklahoma, Inc., UnitedHealthcare of Oregon, Inc., UnitedHealthcare Benefits of Texas, Inc., or UnitedHealthcare of Washington, Inc.