

# Clinical Appropriateness Guidelines

# Genetic Testing for Hereditary Cancer Susceptibility

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# Scope

This document addresses germline genetic testing for hereditary cancer predisposition syndromes. It does not address somatic tumor testing (see Clinical Appropriateness Guidelines for Molecular Testing of Solid and Hematologic Tumors and Malignancies), reproductive testing for hereditary cancer syndromes (see Clinical Appropriateness Guidelines for Genetic Testing for Reproductive Carrier Screening and Prenatal Diagnosis), or polygenic risk scores (see Clinical Appropriateness Guidelines for Genetic Testing for Single-Gene and Multifactorial Conditions). All tests listed in these guidelines may not require prior authorization; please refer to the health plan.

## Genetic Counseling Requirement

Genetic testing included in these guidelines is covered when:

1. The patient meets coverage criteria outlined in the guidelines
2. A recommendation for genetic testing has been made by one of the following:
  - An independent board-certified or board-eligible medical geneticist not employed by a commercial genetic testing laboratory\*
  - An American Board of Medical Genetics or American Board of Genetic Counseling-certified genetic counselor not employed by a commercial genetic testing laboratory\*
  - A genetic nurse credentialed as either a Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APGN) by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC) who is not employed by a commercial genetic testing laboratory\*

Who:

- Has evaluated the case and performed pre-test genetic counseling with the patient or the patient's legal guardian
- Has completed a three-generation pedigree
- Intends to engage in post-test follow-up counseling with the patient or the patient's legal guardian

*\*A physician, genetic counselor or genetic nurse employed by a laboratory that operates within an integrated, comprehensive healthcare delivery system is not considered to be an employee of a commercial genetic testing laboratory for the purpose of these guidelines.*

# Appropriate Use Criteria

Genetic testing for hereditary cancer susceptibility, when the condition is not listed below, is medically necessary when all of the following criteria are met:

- Genetic testing results will impact medical management
- National Comprehensive Cancer Network® (NCCN®) Clinical Practice Guidelines in Oncology (NCCN Guidelines®) include category 1 or 2A, and/or other published management recommendations for an individual who tests positive for the condition/syndrome-specific genes for which testing is being requested
- The individual is the most appropriate person to test or the most appropriate family member is unavailable for testing
- At least one of the following:
  - Individual or unavailable affected family member meets specific testing criteria for at least one of the syndromes listed below
  - Personal and/or family history is consistent with the hereditary cancer syndrome being tested for when that syndrome is not specifically addressed in these guidelines
- Testing method is as targeted as possible (e.g. single gene, known familial pathogenic or likely pathogenic (P/LP) variant, etc.)
- Testing methodology\* has been clinically validated and is the most accurate method unless technical limitations (e.g. poor sample quality) necessitate the need for alternate testing strategies

\*The testing methodology may target DNA and/or RNA.

Single-site testing of familial variants of uncertain significance is not medically necessary.

## Multi-Gene Panel Testing

If not otherwise specified, multi-gene panel testing for hereditary cancer predisposition syndromes described in these guidelines is medically necessary when all of the following criteria are met:

- Genetic testing results will impact medical management **AND**
- Individual meets genetic testing criteria, NCCN Guidelines® or other published clinical diagnostic criteria, for at least one hereditary cancer syndrome (e.g. Hereditary Breast and Ovarian Cancer syndrome, Lynch syndrome, Familial Adenomatous Polyposis, von Hippel Lindau, Cowden syndrome, Li-Fraumeni syndrome) **AND**
- All genes in the panel have peer-reviewed, clinical validity data which have been shown to be associated with the cancer(s) in the personal and/or family history for the individual being tested **AND**
- There are NCCN Guidelines® category 1 or 2A, and/or other published management recommendations for all genes included in the panel

Testing for genes without established clinical validity (e.g. FANCC, MRE11A, RAD50, RECQL4, RINT1, SLX4, XRCC2, GALNT12, SEMA4A, FAN1, ENG, XRCC4, BUB1, BUB3, PTPRJ, EXO1, PMS1) is not medically necessary.

## Germline Testing Following Identification of a Somatic Pathogenic or Likely Pathogenic (P/LP) Variant

Germline testing, after a somatic P/LP variant is identified through the evaluation of solid or hematologic malignancy, is medically necessary when all of the following have been met:

- The variant is pathogenic or likely pathogenic
- There are NCCN Guidelines® category 1 or 2A and/or other published management recommendations specific to P/LP variants in the requested gene
- The P/LP variant is not in one of the genes described below

For P/LP variants in genes in which somatic variants are common but corresponding germline variants are rare (e.g. TP53, PTEN, STK11, and APC), testing is considered medically necessary when the first two above criteria and ANY of the following additional criteria are met:

- Individual meets established testing criteria for the associated hereditary cancer syndrome
- The P/LP variant identified has a high rate of germline incidence
- There is high clinical suspicion based on patient or family history or pathogenic/likely pathogenic allele frequency in tumor sample

## National Comprehensive Cancer Network® (NCCN®) Criteria\*

Genetic testing for the following syndromes is medically necessary when an individual meets the testing criteria outlined in the relevant NCCN® Clinical Practice Guidelines in Oncology:

- Hereditary Colorectal Cancer Syndromes
  - Hereditary Colorectal Cancer syndromes include: Lynch syndrome, Familial adenomatous polyposis (FAP)/Attenuated familial adenomatous polyposis (AFAP), MYH associated polyposis, Juvenile polyposis syndrome, Peutz-Jeghers syndrome, Serrated Polyposis Syndrome
  - Lynch syndrome related cancers for the purpose of evaluating criteria include: colorectal, endometrial, keratoacanthoma, stomach, ovarian, small bowel, urothelial, sebaceous adenoma or carcinoma, hepatobiliary, pancreas, and brain cancer
  - Testing is for genes as listed in NCCN® Genetic/Familial High-Risk Colorectal Cancer, v1.2020
- Hereditary Breast and Ovarian Cancer Syndromes
  - Hereditary Breast and Ovarian Cancer syndromes include: Hereditary Breast and Ovarian Cancer syndrome, Cowden syndrome/PTEN Hamartoma tumor syndrome, Li Fraumeni syndrome, and other breast/ovarian cancer susceptibility syndromes

- Hereditary breast and ovarian cancer syndromes related cancers for the purpose of evaluating criteria include: breast, ovarian, pancreatic and prostate cancer.
- Testing is for susceptibility genes (*high and moderate penetrant genes*) as listed in NCCN<sup>®</sup> Genetic/Familial High-Risk Breast, Ovarian and Pancreatic, v.2.2021
- Multiple Endocrine Neoplasia (type 1 and type 2)
  - Testing is for genes as listed in NCCN<sup>®</sup> Neuroendocrine and Adrenal Tumors, v2.2020
- Diffuse Gastric Cancer
  - Testing is for genes as listed in NCCN<sup>®</sup> Gastric Cancer, v3.2020

### Hereditary Paraganglioma-Pheochromocytoma Syndrome

Single gene testing or a targeted gene panel is medically necessary for hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndrome when all of the following criteria are met:

- Individual meets general criteria for hereditary cancer genetic testing (above)
- Individual with pheochromocytoma or paraganglioma
- Other syndromes and causes of PGL/PCC have been ruled out (e.g., multiple endocrine neoplasia)

Single-site testing is medically necessary for those at risk for a familial deleterious P/LP variant.

### von Hippel-Lindau

Genetic testing is medically necessary for von Hippel-Lindau (VHL) syndrome when an individual meets general criteria for hereditary cancer genetic testing (above) and any one of the following indications:

- At risk individual from a family with a known familial VHL P/LP variant
- Retinal angioma/hemangioblastoma, especially in a young patient
- Spinal or cerebellar hemangioblastoma
- Adrenal or extra-adrenal pheochromocytoma
- Renal cell carcinoma, if the patient is under age 47 years or has a personal or family history of any other tumor typical of VHL
- Multiple renal and pancreatic cysts
- Neuroendocrine tumors of the pancreas
- Endolymphatic sac tumors
- Multiple papillary cystadenomas of the epididymis or broad ligament

Single-site testing is medically necessary for those at risk for a familial deleterious P/LP variant.

# CPT Codes

The following codes are associated with the guidelines in this document. This list is not all inclusive. Medical plans may have additional coverage policies that supersede these guidelines.

Covered when medical necessity criteria are met:

- 81162 BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (ie, detection of large gene rearrangements)
- 81163 BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
- 81164 BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
- 81165 BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
- 81166 BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
- 81167 BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
- 81201 APC (adenomatous polyposis coli) (eg, familial adenomatous polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
- 81202 APC (adenomatous polyposis coli) (eg, familial adenomatous polyposis [FAP], attenuated FAP) gene analysis; known familial variants
- 81203 APC (adenomatous polyposis coli) (eg, familial adenomatous polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants
- 81212 BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
- 81215 BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant

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- 81216 BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
- 81217 BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
- 81288 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
- 81292 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
- 81293 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
- 81294 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
- 81295 MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
- 81296 MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
- 81297 MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
- 81298 MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
- 81299 MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
- 81300 MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
- 81307 PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; full gene sequence
- 81308 PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; known familial variant



- 81317 PMS2 (post meiotic segregation increased 2 [*S. cerevisiae*]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
- 81318 PMS2 (post meiotic segregation increased 2 [*S. cerevisiae*]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
- 81319 PMS2 (post meiotic segregation increased 2 [*S. cerevisiae*]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
- 81321 PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
- 81322 PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant
- 81323 PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant
- 81351 TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; full gene sequence
- 81352 TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; targeted sequence analysis (eg, 4 oncology)
- 81353 TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; known familial variant
- 81432 Hereditary breast cancer-related disorders (eg, 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 (eg, 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 syndromes (eg, Lynch syndrome, familial adenomatous polyposis); genomic sequence analysis panel, must include analysis of at least 7 genes, including APC, CHEK2, MLH1, MSH2, MSH6, MUTYH, and PMS2
- 81436 Hereditary colon cancer syndromes (eg, Lynch syndrome, familial adenomatous polyposis); duplication/deletion gene analysis panel, must include analysis of at least 8 genes, including APC, MLH1, MSH2, MSH6, PMS2, EPCAM, CHEK2, and MUTYH

- 81437 Hereditary neuroendocrine tumor disorders (eg, 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 (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL
- 0129U Hereditary breast cancer–related disorders (eg, 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)

Codes that do not meet medical necessity criteria:

- 0101U Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatous polyposis), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated (15 genes [sequencing and deletion/duplication], EPCAM and GREM1 [deletion/duplication only])
- 0102U Hereditary breast cancer-related disorders (eg, 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 (eg, 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])
- 0130U-  
0138U +RNAInsight™ (Ambry Genetics®)
- 0157U APC (APC regulator of WNT signaling pathway) (eg, familial adenomatous polyposis [FAP]) mRNA sequence analysis (List separately in addition to code for primary procedure) (Use 0157U in conjunction with 81201)
- 0158U MLH1 (mutL homolog 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure) (Use 0158U in conjunction with 81292)
- 0159U MSH2 (mutS homolog 2) (eg, hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure) (Use 0159U in conjunction with 81295)

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- 0160U MSH6 (mutS homolog 6) (eg, hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure) (Use 0160U in conjunction with 81298)
- 0161U PMS2 (PMS1 homolog 2, mismatch repair system component) (eg, hereditary nonpolyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure) (Use 0161U in conjunction with 81317)
- 0162U Hereditary colon cancer (Lynch syndrome), targeted mRNA sequence analysis panel (MLH1, MSH2, MSH6, PMS2) (List separately in addition to code for primary procedure) (Use 0162U in conjunction with 81292, 81295, 81298, 81317, 81435)
- 0235U PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
- 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
- ANY Myriad myRisk® (Myriad Genetics, Inc.)
- ANY CancerNext® (Ambry Genetics®)
- ANY Comprehensive Cancer Panel (GeneDx)

## Background

Cancer is the result of genetic alterations that often result in the deregulation of pathways that are important for various cellular functions including growth, cell cycle progression, and apoptosis (programmed cell death), among others. While most genetic P/LP variants identified within a tumor are acquired, there are several cancer predisposition syndromes caused by inherited germline P/LP variants. Many of these, such as Hereditary Breast and Ovarian Cancer Syndrome associated with BRCA1 and BRCA2, are well-described with consensus recommendations for genetic testing and management. Others, however, have been recently identified and testing criteria and management recommendations are not well established.

*See relevant NCCN Guidelines® for background related to Lynch syndrome, Familial adenomatous polyposis (FAP)/Attenuated familial adenomatous polyposis (AFAP), MYH-associated polyposis, Hereditary breast, ovarian, and pancreatic cancer susceptibility syndromes, Juvenile polyposis syndrome, Peutz-Jeghers syndrome, Cowden syndrome/PTEN Hamartoma tumor syndrome, Li Fraumeni syndrome, Multiple endocrine neoplasia type 1 (MEN1), Multiple endocrine neoplasia type 2 (MEN2A and 2B), and Diffuse gastric cancer.*

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## Rationale for Genetic Counseling for Hereditary Cancer Conditions

Pre-test genetic counseling provides individuals seeking genetic testing the opportunity to make informed decisions about their genetic testing and subsequent medical management options. Genetic counseling combines expertise in obtaining and interpreting family history information, the ability to identify the most beneficial individual in a family to initiate testing, identification of the most appropriate testing options, experience in obtaining informed consent for testing and proficiency in genetic variant interpretation, in order to maximize the genetic testing experience for patients and their healthcare providers. The genetic counseling informed consent process also educates and empowers patients to consider the psychological, financial, employment, disability, and insurance implications of genetic testing and results (Al-Khatib et al. 2018). Patients who receive genetic counseling report increased knowledge, understanding, and satisfaction regarding their genetic testing experience (Armstrong et al. 2015; Harvey et al. 2007).

The advent of multi-gene panels and genome-scale sequencing have increased the complexity of the genetic testing landscape. Misuse of genetic testing increases the risk for adverse events and patient harm, including missed opportunities for diagnosis and disease prevention (Bellcross et al. 2011; Plon et al. 2011; Farmer et al. 2019). Genetic information requires expert interpretation and ongoing re-evaluation to ensure the most accurate interpretation is utilized to inform medical management decision making. The multitude of genetic testing options as well as the complex information revealed by genetic testing can make choosing the most appropriate test and interpretation of results difficult for non-genetics healthcare providers (Ray 2011). Involvement of a clinical genetics provider has been shown to ensure the correct test is ordered, limit result misinterpretation and allow patients to make informed, evidence-based medical decisions with their healthcare providers (Cragun et al. 2015; Farmer et al. 2019).

Genetic counseling not only improves patient outcomes but also reduces unnecessary healthcare spending. Pre-test genetic counseling has been shown to reduce inappropriate test ordering and prevent unnecessary medical procedures and interventions that follow from inaccurate result interpretation (DHHS 2011). While genetic testing is now available for almost all clinical specialties, correct use and interpretation is necessary to prevent adverse outcomes. While genetic counseling may benefit any patient considering or undergoing genetic testing, tests that offer predictive information or have a higher chance of identifying variants of uncertain significance often carry stronger recommendations in the form of consensus guidelines and professional statements recommending genetic counseling by trained genetics professionals.

Many consensus organizations including the American Society of Clinical Oncology (ASCO) (Robson et al. 2015), the National Comprehensive Cancer Network® (NCCN®)\* the American College of Obstetricians and Gynecologists (ACOG 2017) and the U.S. Preventive Services Task Force (USPSTF) (Moyer 2014) recommend genetic counseling as an integral part of the evaluation of individuals at risk for hereditary cancer susceptibility syndromes. Additionally, the Patient Protection and Affordable Care Act (2010) has established that counseling prior to P/LP variant testing is an established essential health benefit appropriate for individuals with breast cancer.

Per the NCCN®, cancer risk assessment and genetic counseling by a cancer genetics professional is highly recommended when genetic testing is offered (ie, pre-test counseling) and after results are disclosed (ie, post-test counseling), with assurance that the pre-test counseling includes collection of a comprehensive family history, evaluation of risk, full genetic differential review and education for the patient on the outcomes of testing, as well as full informed consent.

The American Society of Clinical Oncologists (ASCO) (Robson et al. 2015) additionally recognizes that multi-gene testing for hereditary cancer susceptibility is currently challenged by uncertainties and areas of needed study, and thus recommend that this testing is ideally handled by providers who are well educated on the complex nature of this genetic testing. Additional note is made that evidence has suggested that overinterpretation of variants identified in these panels by non-expert providers may harm patient care, such as inappropriate medical interventions and psychological stress. Thus, since 1996 ASCO has recommended that pre-test counseling for hereditary predisposition testing includes, at minimum: details on the purpose of testing, potential outcomes, implications for the patient and their family members, risks associated with the genes being tested, costs associated, psychological implications, risks and protections for genetic discrimination, confidentiality issues related to genetic testing, research use of samples, alternate options to testing, utility of medical surveillance and prevention, importance of sharing results with at risk relatives, follow up planning for results, rate of variants of uncertain significance, as well as contrast of high penetrance to low penetrance genes. While steps are being made to improve knowledge gaps, ASCO recognizes that the level of knowledge of genetics needed by oncologists “exceeds what most received during training.” Because of the complex nature of germline genetic testing (both targeted and panel-based), and the time required for these discussions, ASCO states “it is particularly important that providers with particular experience in the assessment of inherited cancer risk be involved in the ordering and interpretation of these tests.”

### **Germline testing following identification of a somatic pathogenic or likely pathogenic (P/LP) variant**

As tumor testing, especially broad molecular profiling, becomes more common, it is expected that there will be an increase in the number of somatic P/LP variants identified in genes associated with hereditary cancer syndromes. In most cases, this is associated with a risk that a germline P/LP variant will be identified, but with certain cancer types and genes, the likelihood of an underlying germline P/LP variant remains low. In addition, many types of tumors have a high rate of variation in genes associated with hereditary cancer syndromes, but unrelated to the same tumor type. An often-cited example of this is the high-rate of APC P/LP variants identified in endometrial cancer, despite the fact that germline P/LP variants in APC are not associated with an increased risk of endometrial cancer.

Several studies have shown that the prevalence of pathogenic germline variants among those in whom somatic variants have been identified is high enough to consider germline testing in most actionable genes (Catenacci et al. 2015; Schrader et al. 2016). One of the largest studies to date, using the Foundation Medicine platform, predicted that variants in high-risk cancer genes were likely pathogenic or pathogenic in 3.1 to 7% of tumor samples tested; however, the study design did not compare the tumor DNA to normal. Additionally, this study noted the rate of germline P/LP variants varies widely by tissue type and gene (Hall 2015). It has been noted that identification of TP53, STK11, PTEN and APC in tumor tissue are less likely to be associated with germline P/LP variants (Jain et al. 2016). For instance, TP53 variants are identified in almost 85% of ovarian tumors (COSMIC data), but fewer than 3% of patients with apparently hereditary ovarian cancer syndromes will test positive for a TP53 P/LP variant. Therefore, additional factors, such as clinical presentation, family history, or data obtained from variant databases regarding likelihood of a germline origin should be considered when determining medical necessity of germline testing for these actionable genes.

### **Hereditary Paraganglioma-Pheochromocytoma Syndrome**

Hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes are characterized by paragangliomas (tumors that arise from neuroendocrine tissues symmetrically distributed along the paravertebral axis from the base of the skull to the pelvis) and by pheochromocytomas (paragangliomas that are confined to the adrenal medulla). Extra-adrenal parasymphathetic

paragangliomas are located predominantly in the skull base, neck, and upper mediastinum; approximately 95% of such tumors are non-secretory. In contrast, sympathetic extra-adrenal paragangliomas are generally confined to the lower mediastinum, abdomen, and pelvis, and are typically secretory. Pheochromocytomas, which arise from the adrenal medulla, typically hypersecrete catecholamines.

Hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes should be considered in all individuals with paragangliomas and/or pheochromocytomas, particularly those with tumors that are: multiple (i.e., >1 paraganglioma or pheochromocytoma), including bilateral adrenal pheochromocytoma; multifocal with multiple synchronous or metachronous tumors; recurrent; or early onset (i.e., age <45 years) (Young et al. 2011; Fishbein et al. 2013; Lenders et al. 2014; Muth et al. 2019).

Several genes are reported to cause Hereditary PCC/PGL syndromes, however some are more common than others. The genes most commonly associated with hereditary PCC/PGL are SDHA, SDHB, SDHC and SDHD. In addition, there are other known hereditary cancer syndromes in which pheochromocytomas may occur. Typically, in adults, targeted or sequential testing can be performed, as enough symptoms are present to target genetic testing. However, in young children where a PCC or PGL is the only symptom, targeted testing may not be possible. Research has also indicated that those with noradrenergic tumors are at a higher risk for P/LP variants in a wide variety of genes including MDH2 and HIF2A (Gupta 2017). In certain scenarios, testing with a targeted panel is reasonable.

### **von Hippel-Lindau**

Von Hippel-Lindau (VHL) disease is characterized by abnormal growth of blood vessels, which can lead to hemangioblastomas of the brain, spinal cord and retinas; renal cysts and clear cell renal carcinomas; pheochromocytomas; and endolymphatic sac tumors. P/LP variants in the VHL gene are inherited in an autosomal dominant manner. It is estimated that 80% of individuals with VHL inherited it from an affected parent, and approximately 20% are due to new or de novo P/LP variants (van Leeuwen et al. 2019).

Although clinical diagnosis is possible, molecular confirmation is recommended to confirm the diagnosis in patients not fully meeting diagnostic criteria and to facilitate screening in asymptomatic/pre-symptomatic relatives, including at-risk children (Nielsen et al. 2016).

## **Professional Society Guidelines**

### **American College of Obstetricians and Gynecologists (ACOG)**

ACOG Practice Bulletin No. 793. Hereditary Cancer Syndromes and Risk Assessment.

*Obstet Gynecol.* 2019 Dec;134(6): e143-e149. PubMed PMID: 31764758.

### **American College of Medical Genetics and Genomics (ACMG)**

ACMG Statement. Points to Consider: Is There Evidence to Support BRCA1/2 and Other Inherited Breast Cancer Genetic Testing for All Breast Cancer Patients?

Pal T, Agnese D, Daly M, La Spada A, Litton J, Wick M, Klugman S, Esplin ED, Jarvik GP; Professional Practice and Guidelines Committee. *Genet Med.* 2020 Apr;22(4):681-685. PubMed PMID: 31831881.

### **American Society of Clinical Oncology (ASCO)**

Policy Statement Update. Genetic and Genomic Testing for Cancer Susceptibility.

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Robson ME, Bradbury AR, Arun B, et al. *J Clin Oncol*. 2015 Nov 1; 33(31):3660-7. PubMed PMID: 26324357.

## Endocrine Society

Clinical Practice Guideline. Pheochromocytoma and Paraganglioma

Lenders JW, Duh QY, Eisenhofer G, et al. *J Clin Endocrinol Metab*. 2014 Jun;99(6):1915–42. PubMed PMID: 24893135.

## Joint Statements

ACOG Practice Bulletin No. 182. Hereditary Breast and Ovarian Cancer Syndrome. ACOG and Society of Gynecologic Oncology.

*Obstet Gynecol*. 2017 Sep;130(3):657-659. PubMed PMID: 28832475.

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<http://www.nccn.org/index.asp>.\*

- Gastric Cancer. (Version 3.2020). Accessed September 9, 2020.
- Genetic/Familial High-Risk Assessment: Colorectal (Version 1.2020). Accessed September 9, 2020.
- Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic (Version 2.2021). Accessed December 9, 2020.
- Neuroendocrine Tumors and Adrenal Tumors (Version 2.2020). Accessed September 9, 2020.

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# Selected References

- 1 Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Heart Rhythm*. 2018 Oct;15(10): e190-e252. Epub 2017 Oct 30. PubMed PMID 29097320.
- 2 Angeli D, Salvi S, Tedaldi G. Genetic predisposition to breast and ovarian cancers: How many and which genes to test? *Int J Mol Sci*. 2020 Feb 8;21(3). PubMed PMID: 32046255.
- 3 Armstrong J, Toscano M, Kotchko N, et al. Utilization and Outcomes of BRCA Genetic Testing and Counseling in a National Commercially Insured Population: The ABOUT Study. *JAMA Oncol*. 2015 Dec;1(9):1251-60. PubMed PMID: 26426480.
- 4 Baysal BE, Willett-Brozick JE, Lawrence EC, et al. Prevalence of SDHB, SDHC, and SDHD germline mutations in clinic patients with head and neck paragangliomas. *J Med Genet*. 2002; 39:178–83. PubMed PMID: 11897817.

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- 5 Bean LJH, Funke B, Carlston CM, Gannon JL, Kantarci S, Krock BL, Zhang S, Bayrak-Toydemir P, on behalf of the ACMG Laboratory Quality Assurance Committee. Diagnostic gene sequencing panels: from design to report- a technical standard of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2019 Nov 16. PubMed PMID: 31732716.
- 6 Bellcross CA, Kolor K, Goddard K, Coates RF, Reyes M, Khoury MJ. Awareness and utilization of BRCA1/2 testing among U.S. primary care physicians. *Am J Prev Med*. 2011; 40:61–66. PubMed PMID: 21146769.
- 7 Bhalla A, Saif MW. PARP-inhibitors in BRCA-associated pancreatic cancer. *JOP*. 2014 Jul 28;15(4):340-3. PubMed PMID: 25076338.
- 8 Binderup MLM, Stendell AS, Galanakis M, Møller HU, Kiilgaard JF, Bisgaard ML. Retinal hemangioblastoma: prevalence, incidence and frequency of underlying von Hippel-Lindau disease. *Br J Ophthalmol*. 2018 Jul;102(7):942-947. Epub 2017 Sep 28. PubMed PMID: 28972023.
- 9 Castro-Vega LJ, Buffet A, De Cubas AA, et al. Germline mutations in FH confer predisposition to malignant pheochromocytomas and paragangliomas. *Hum Mol Genet*. 2014 May 1;23(9):2440-6. Epub 2013 Dec 13. PubMed PMID: 24334767.
- 10 Catenacci DV, Amico AL, Nielsen SM, Geynisman DM, Rambo B, Carey GB, Fackenthal J, Marsh RD, Kindler HL, Olopade OI. Tumor genome analysis includes germline genome: are we ready for surprises? *Int J Cancer*. 2015 Apr 1;136(7):1559-67. PubMed PMID: 25123297.
- 11 Clark GR, Sciacovelli M, Gaude E, et al. Germline FH mutations presenting with pheochromocytoma. *J Clin Endocrinol Metab*. 2014 Oct;99(10):E2046-50. Epub 2014 Jul 8. PubMed PMID: 25004247.
- 12 Cragun D, Camperlango L, Robinson E, Caldwell M, Kim J, Phelan C, Monteiro AN, Vadaparampil ST, Sellers TA, Pal T. Differences in BRCA counseling and testing practices based on ordering provider type. *Genet Med*. 2015 Jan;17(1):51-7. PubMed PMID 24922460.
- 13 Decker J, Neuhaus C, Macdonald F, et al. Clinical utility gene card for: von Hippel-Lindau (VHL). *Eur J Hum Genet*. 2014 Apr;22(4). Epub 2013 Aug 28. PubMed PMID: 23982691.
- 14 Desmond A, Kurian AW, Gabree M, Mills MA, et al. Clinical actionability of multigene panel testing for hereditary breast and ovarian cancer risk assessment. *JAMA Oncol*. 2015 Oct;1(7):943-951. PubMed PMID: 26270727.
- 15 Easton DF, Pharoah PD, Antoniou AC, et al. Gene-panel sequencing and the prediction of breast-cancer risk. *N Engl J Med*. 2015 Jun 4;372(23):2243-2257. PubMed PMID: 26014596.
- 16 Else T, Greenberg S, Fishbein L. Hereditary Paraganglioma-Pheochromocytoma Syndromes. 2008 May 21 [Updated 2018 Oct 4]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. *GeneReviews* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1548/>.
- 17 Farmer MB, Bonadies DC, Mahon SM, et al. Adverse Events in Genetic Testing: The Fourth Case Series. *Cancer J*. 2019 Jul/Aug;25(4):231-236. PubMed PMID: 31335384.
- 18 Filippini SE, Vega A. Breast cancer genes: beyond BRCA1 and BRCA2. *Front Biosci (Landmark Ed)*. 2013 Jun 1; 18:1358-72. PubMed PMID: 2374889.
- 19 Fishbein L, Merrill S, Fraker DL, et al. Inherited mutations in pheochromocytoma and paraganglioma: why all patients should be offered genetic testing. *Ann Surg Oncol*. 2013 May;20(5):1444-1450. PubMed PMID: 23512077.
- 20 Goggins M, Overbeek KA, Brand R, et al. International Cancer of the Pancreas Screening (CAPS) consortium. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium. *Gut*. 2020 Jan;69(1):7-17. PubMed PMID: 31672839.
- 21 Gómez-Graña A, Pollard PJ, Rustin P, et al. Germline mutations in FH confer predisposition to malignant pheochromocytomas and paragangliomas. *Hum Mol Genet*. 2014 May 1;23(9):2440-6. Epub 2013 Dec 13. PubMed PMID: 24334767.
- 22 Gupta G, Pacak K. Precision medicine: an update of genotype-biochemical phenotype relationships in pheochromocytoma/paraganglioma patient. *Endocr Pract*. 2017 Jun;23(6):690-704. Epub 2017 Mar 23. PubMed PMID: 28332883.
- 23 Hall MJ, Daly MB, Ross EA, et al. Germline variants in cancer risk genes detected by NGS-based comprehensive tumor genomic profiling (CGP) [abstract]. *J Clin Oncol* 2015;33(Suppl): Abstract 11084.
- 24 Harvey EK, Fogel CE, Peyrot M, et al. Providers' knowledge of genetics: A survey of 5915 individuals and families with genetic conditions. *Genet Med* 2007. 9(5):259-267. PubMed PMID: 17505202.
- 25 Jain R, Savage M, Forman A, Mukherji R, Hall MJ. The Relevance of hereditary cancer risks to precision oncology: what should providers consider when conducting tumor genomic profiling? *J Natl Compr Canc Netw* 2016;14(6):795–806. PubMed PMID: 27283171.
- 26 Kanchi K, Johnson K, Lu C, et al. Integrated analysis of germline and somatic variants in ovarian cancer. *Nat Commun*. 2014; 5:3156. PubMed PMID: 24448499.
- 27 LaDuca H, Polley EC, Yussuf A, et al. A clinical guide to hereditary cancer panel testing: evaluation of gene-specific cancer associations and sensitivity of genetic testing criteria in a cohort of 165,000 high-risk patients. *Genet Med*. 2019 Aug 13. Doi: 10.1038/s41436-019-0633-8. [Epub ahead of print] PubMed PMID: 31406321.
- 28 Lee K, Seifert BA, Shimelis H, et al. Clinical validity assessment of genes frequently tested on hereditary breast and ovarian cancer susceptibility sequencing panels. *Genet Med*. 2019 Jul;21(7):1497-1506. PubMed PMID: 30504931.
- 29 Moyer VA; U.S. Preventive Services Task Force. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*. 2014 Feb 18;160(4). PubMed PMID: 24366376.
- 30 Muth A, Crona J, Gimm O, et al. Genetic testing and surveillance guidelines in hereditary pheochromocytoma and paraganglioma. *J Intern Med*. 2019 Feb;285(2):187-204. PubMed PMID: 30536464.
- 31 Nielsen SM, Rhodes L, Blanco I, Chung WK, Eng C, Maher ER, Richard S, Giles RH. von Hippel-Lindau Disease: genetics and role of genetic counseling in a multiple neoplasia syndrome. *J Clin Oncol*. 2016 Jun 20;34(18): 2172-81. Epub: 2016 Apr 25. PubMed PMID: 27114602.
- 32 Norquist BM, Harrell MI, Brady MF, et al. Inherited mutations in women with ovarian carcinoma. *JAMA Oncol*. 2016 Apr;2(4):482-90. PubMed PMID: 26720728.
- 33 O'Leary E, Iacoboni D, Holle J, et al. Expanded gene panel use for women with breast cancer: Identification and intervention beyond breast cancer risk. *Ann Surg Oncol*. 2017 Oct;24(10):3060-3066. PubMed PMID: 28766213.
- 34 Patient Protection and Affordable Care Act, 42 U.S.C. §18001 (2010).

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- 35 Plon SE, Cooper HP, Parks B, Dhar SU, Kelly PA, Weinberg AD, Staggs S, Wang T, Hilsenbeck S. Genetic testing and cancer risk management recommendations by physicians for at-risk relatives. *Genet Med*. 2011; 13:148–154. PubMed PMID: 21224735.
- 36 Ramus SJ, Song H, Dicks E, et al. Germline mutations in the BRIP1, BARD1, PALB2, and NBN genes in women with ovarian cancer. *J Natl Cancer Inst*. 2015 Aug 27;107(11). pii: djv214. PubMed PMID: 26315354.
- 37 Ray T. “Cleveland Clinic Explores Issues Associated with Integrating Genomics into Healthcare.” *GenomeWeb*. Mar 11, 2011. Accessed Nov 19, 2018.
- 38 Robson ME, Bradbury AR, Arun B, Domchek SM, Ford JM, Hampel HL, et al. American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility. *J Clin Oncol*. 2015 Nov 1;33(31):3660-7. PubMed PMID: 26324357.
- 39 Rosenthal ET, Bernhisel R, Brown K, et al. Clinical testing with a panel of 25 genes associated with increased cancer risk results in a significant increase in clinically significant findings across a broad range of cancer histories. *Cancer Genet*. 2017 Dec;218-219:58-68. PubMed PMID: 29153097.
- 40 Seifert BA, McGlaughon JL, Jackson SA, et al. Determining the clinical validity of hereditary colorectal cancer and polyposis susceptibility genes using the Clinical Genome Resource Clinical Validity Framework. *Genet Med*. 2019 Jul;21(7):1507-1516. PubMed PMID: 30523343.
- 41 Shrader KA, Cheng DT, Joseph V, Prasad M, Walsh M, Zehir A, Ni A, Thomas T, Benayed R, Ashraf A, Lincoln A, Arcila M, Stadler Z, Solit D, Hyman DM, Zhang L, Klimstra D, Ladanyi M, Offit K, Berger M, Robson M. Germline variants in targeted tumor sequencing using matched normal DNA. *JAMA Oncol*. 2016 Jan;2(1):104-11. PubMed PMID: 26556299.
- 42 Song H, Dicks E, Ramus SJ, et al. Contribution of germline mutations in the RAD51B, RAD51C, and RAD51D genes to ovarian cancer in the population. *J Clin Oncol*. 2015 Sep 10;33(26):2901-2907. PubMed PMID: 26261251.
- 43 Stanich PP, Pearlman R, Hinton A, et al. Prevalence of germline mutations in polyposis and colorectal cancer-associated genes in patients with multiple colorectal polyps. *Clin Gastroenterol Hepatol*. 2019 Sep;17(10):2008-2015.e3. PubMed PMID: 30557735.
- 44 Susswein LR, Marshall ML, Nusbaum R, et al. Pathogenic and likely pathogenic variant prevalence among the first 10,000 patients referred for next-generation cancer panel testing. *Genet Med*. 2016 Aug;18(8):823-832. Erratum in: *Genet Med*. 2016 May;18(5):531-2. PubMed PMID: 26681312.
- 45 Taylor A, Brady AF, Frayling IM, et al; UK Cancer Genetics Group (UK-CGG). Consensus for genes to be included on cancer panel tests offered by UK genetics services: guidelines of the UK Cancer Genetics Group. *J Med Genet*. 2018 Jun;55(6):372-377. PubMed PMID: 29661970.
- 46 Toss A, Tomasello C, Rassaboni E, et al. Hereditary ovarian cancer: not only BRCA 1 and 2 genes. *Biomed Res Int*. 2015; 2015:341723. Epub 2015 May 17. PubMed PMID: 26075229.
- 47 Tung N, Domchek SM, Stadler Z, et al. Counselling framework for moderate-penetrance cancer-susceptibility mutations. *Nat Rev Clin Oncol*. 2016 Sep;13(9):581-588. PubMed PMID: 27296296.
- 48 United States, Department of Health and Human Services Secretary’s Advisory Committee. Report of the Secretary’s Advisory Committee on Genetics, Health, and Society. [Internet] February 2011 [cited November 2018]. Available from: <https://osp.od.nih.gov/sacghsdocs/genetics-education-and-training-report-of-the-secretarys-advisory-committee-on-genetics-health-and-society/>.
- 49 van Leeuwen RS, Ahmad S, Links TP, et al. Von Hippel-Lindau Syndrome. 2000 May 17 [Updated 2018 Sep 6]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. *GeneReviews* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK1463/>.
- 50 Walsh T, Casadei S, Coats KH, et al. Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. *JAMA* 2006; 295:1379-88. PubMed PMID: 16551709.
- 51 Young WF Jr, Abboud AL. Editorial: paraganglioma - all in the family. *J Clin Endocrinol Metab*. 2006; 91:790–2. PubMed PMID: 16522703.

# Revision History

## Medical Advisory Board Review:

- v1.2021 11/13/2020: Approved
- v3.2020 11/13/2020: Approved
- v2.2020 05/08/2020: Reviewed
- v1.2020 11/04/2019: Approved
- v2.2019 05/23/2019: No Criteria Changes
- v1.2019 11/07/2018: Reviewed
- v1.2018 03/31/2018: Reviewed

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**Clinical Steering Committee Review:**

v1.2021 10/13/2020: Approved  
 v3.2020 10/13/2020: Approved  
 v2.2020 04/06/2020: Approved  
 v1.2020 10/11/2019: Approved  
 v3.2019 12/09/2019: Approved  
 v2.2019 05/20/2019: Approved  
 v1.2019 10/03/2018: Approved  
 v1.2018 02/28/2018: Approved  
 v3.2017 11/01/2017: Approved  
 v2.2017 05/03/2017: Approved  
 v1.2017 01/25/2017: Approved

**Revisions:**

Version	Date	Editor	Description
v1.2021	9/11/2020	Stefanie Finch, MS, CGC and Eleanor Riggs, MS, CGC	Semi-annual review. Genetic counseling requirements were updated. Reformatted NCCN® criteria. Updated CPT codes, professional society guidelines, background and references.
v3.2020	10/9/2020	Eleanor Riggs, MS, CGC	Interim Update: NCCN Guidelines® Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (Version 1.2021) was updated. CPT codes were updated.
v2.2020	03/13/2020	Eleanor Riggs, MS, CGC	Semi-annual review. The Multi-Gene Panel Testing criteria was updated, i.e. removal of MSH3 from the list of genes without established clinical validity. Removed CHEK2, PALB2 and prostate cancer criteria. Updated professional society guidelines, background and references.
	07/24/2020	Carrie Langbo, MS, CGC	NCCN Guidelines® were accessed for inclusion of the most recent published version.
v1.2020	09/11/2019	Eleanor Riggs, MS, CGC	Semi-annual review. Revisions were made to multi-gene panel testing criteria, corrections were made to CHEK2 and PALB2 criteria and Prostate Cancer

	2/5/2020	Carrie Langbo, MS, CGC	<p>criteria was updated. CPT codes, background, Professional Society/NCCN® guidelines and references were updated.</p> <p>NCCN Guidelines® were accessed for inclusion of the most recent published version. Minor revisions to text were incorporated based on updated Guidelines but did not impact coverage criteria/necessitate MAB/CSC review.</p>
v3.2019	12/9/2019	Carrie Langbo, MS, CGC	Interim Update: Revisions made to multi-gene panel testing criteria and approved by the PAB on 11/04/2019 and the CSC on 10/11 and 12/09/2019 are being published as an interim update, prior to the anticipated March 3, 2020 effective date, in order to accommodate recent revisions to NCCN® Guideline, Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic (v1.2020).
v2.2019	05/17/2019  07/25/2019	Michele Gabree, MS, CGC  Carrie Langbo, MS, CGC	<p>Semi-annual review. No criteria changes. Text clarification made for prostate cancer germline testing. Updated references.</p> <p>NCCN Guidelines® were accessed for inclusion of the most recent published version. Minor revisions to text were incorporated based on updated Guidelines but did not impact coverage criteria/necessitate MAB/CSC review.</p>
v1.2019	11/01/2018	Sheri Babb, MS, CGC	Semi-annual review. Criteria added for germline testing after somatic mutation is identified. NCCN® category 2B criteria recommendations were removed from general statements of medical necessity. Criteria revisions for CHEK2 and PALB2. Background revised. Renumbered to 2019. Professional Society/NCCN Guidelines® and references updated. Administrative change to genetic counseling requirement - moved from client policy to guidelines. Reformatted CPT code list. PMID added.

v1.2018	03/31/2018	Gwen Fraley, MS, CGC	Semi-annual review. Criteria added for germline testing for prostate cancer indications. Background revised. Renumbered to 2018. Professional Society/NCCN Guidelines® and references updated. Disclaimer sentence added to Scope section. Appropriate symbols ( $\leq$ ) inserted for PALB2, CHEK2 criteria.
v3.2017	11/1/2017	Sheri Babb, MS, CGC	Revised criteria for VHL. Updated background and references. Renumbered to v3.2017. Submitted to CSC for approval.
v2.2017	09/28/2017	Megan Czarniecki, MS, CGC	Formatted references to NLM style. Moved methodological considerations to appropriate use criteria and background. Updated associated CPT codes. Removed genetic counseling recommendation. Approved by Policy Lead.
v2.2017	07/03/2017	Denise Jones, MS, CGC	Quarterly review. No criteria changes. Updated references.
v2.2017	05/03/2017	Gwen Fraley, MS, CGC	Expanded PGL/PCC criteria to include panels. Updated references.
v1.2017	01/23/2017	Heather Dorsey, MS, CGC	Quarterly review. No criteria changes. Updated references. Renumbered to 2017.
v1.2016	05/24/2016	Marie Schuetzle, MS, CGC	Added PALB2 and CHEK2 criteria. Updated references.
v1.2015	05/07/2015	Marie Schuetzle, MS, CGC	Original version

**Original Effective Date:** 05/07/2015

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