

## **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). All tests listed in these guidelines may not require prior authorization; please refer to 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 individual and performed pre-test genetic counseling
- Has completed a three-generation pedigree
- Intends to engage in post-test follow-up counseling

*\*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

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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 mutation, etc.)

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

### **Multi-Gene Panel Testing**

Multi-gene panel testing for the hereditary cancer susceptibility syndromes described in these guidelines is medically necessary when all of the following criteria are met:

- Genetic testing results will impact medical management
- Individual meets genetic testing criteria for BRCA1/2 and one other syndrome, or individual meets criteria for three hereditary cancer susceptibility syndromes
- All genes in the panel are relevant to the personal and family history for the individual being tested
- There are NCCN Guidelines® category 1 or 2A, and/or other published management recommendations for all genes included in the panel

### **Germline Testing Following Identification of a Somatic Mutation**

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

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

For mutations in genes in which somatic mutations are common but corresponding germline mutations are rare (i.e. 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 mutation 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 (NCCN Guideline®), (Gastric Cancer, v2.2018; Genetic/Familial High-Risk Assessment: Colorectal, v1.2018; Genetic/Familial High-Risk Assessment: Breast and Ovarian, v2.2019; Prostate v4.2018; Neuroendocrine Tumors, v2.2018):

- Lynch syndrome: MLH1, MSH2, MSH6, PMS2, EPCAM  
Cancers considered to be Lynch syndrome related cancers for purposes of evaluating criteria below are: colorectal, endometrial, keratoacanthoma, stomach, ovarian, small bowel, ureter or renal pelvis, sebaceous adenoma or carcinoma, hepatobiliary, pancreas, brain cancer.
- Familial adenomatous polyposis (FAP)/Attenuated familial adenomatous polyposis (AFAP): APC
- MYH-associated polyposis: MYH
- Hereditary breast and ovarian cancer syndrome: BRCA1, BRCA2
- Cancers considered to be related to hereditary breast and ovarian cancer syndromes for the purposes of evaluating criteria also include pancreatic and prostate cancer
- Juvenile polyposis syndrome: BMPR1A, SMAD4
- Peutz-Jeghers syndrome: STK11
- Cowden syndrome/PTEN Hamartoma tumor syndrome: PTEN
- Li Fraumeni syndrome: TP53
- Multiple endocrine neoplasia type 1: MEN1
- Multiple endocrine neoplasia type 2: MEN types 2A and 2B, RET
- Diffuse gastric cancer: CDH1

## CHEK2

CHEK2 genetic testing is medically necessary when the individual meets general criteria for hereditary cancer genetic testing (as above) and one of the following criteria are met:

- Personal history of female breast cancer diagnosed  $\leq 45$
- Personal history of female breast cancer diagnosed at or under age 50 with one of the following:
  - Additional primary breast cancer at any age
  - One first or second degree relative (male or female) with breast cancer at any age

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- An unknown or limited family history, defined as fewer than two first or second degree female relatives in either lineage surviving beyond 60
- Personal history of female breast cancer diagnosed at any age with one of the following:
  - One first or second degree blood relative with breast cancer  $\leq 50$  or male breast cancer at any age
  - Two first or second degree blood relatives on the same side of the family with breast cancer at any age
- Personal history of male breast cancer at any age with at least 1 first or second degree relative with breast cancer at any age
- Family history includes either of the following:
  - Individual has a first or second degree blood relative who meets any of the above CHEK2 criteria
  - At risk individual from a family with a known familial CHEK2 mutation

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

Single gene testing or 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 mutation.

### **Prostate Cancer**

Genetic testing of BRCA1/2, ATM and PALB2 are medically necessary for individuals with localized stage III (NCCN® high-risk and very high-risk group), regional or metastatic prostate cancer.

### **PALB2**

PALB2 genetic testing is medically necessary when the individual meets general criteria for hereditary cancer genetic testing (as above) and one of the following criteria are met:

- Personal history of female breast cancer diagnosed  $\leq 45$
- Personal history of female breast cancer diagnosed at or under age 50 with at least one of the following:
  - Additional primary breast cancer at any age
  - One first or second degree blood relative with
    - Pancreatic cancer, or

- Breast cancer at  $\leq 50$ , or
    - Male breast cancer, or
    - Two primary breast cancers at any age
  - Two first or second degree blood relatives on the same side of the family with breast cancer at any age
  - An unknown or limited family history (i.e., fewer than two first or second degree female blood relatives in either lineage surviving beyond age 60 years)
- Personal history of female breast cancer diagnosed with two primary breast cancers with one of the following:
  - One first or second degree blood relative with
    - Pancreatic cancer, or
    - Male breast cancer, or
    - Breast cancer at  $\leq 50$ , or
    - Two primary breast cancers
  - Two first or second degree blood relatives on the same side of the family with breast cancer at any age
- Personal history of female breast cancer diagnosed at any age with at least one of the following:
  - Two first or second degree blood relatives on the same side of the family with at least one of the following:
    - Breast cancer at any age (male or female), or
    - Two primary breast cancers, or
    - Pancreatic cancer
  - Three first or second degree blood relatives with pancreatic cancer or breast cancer at any age
- Personal history of male breast cancer at any age with at least one of the following:
  - One first or second degree blood relative with
    - Pancreatic cancer, or
    - Male breast cancer, or
    - Breast cancer  $\leq 50$ , or
    - Two primary breast cancers at any age
  - Two first or second degree blood relatives on the same side of the family with breast cancer at any age
- Personal history of pancreatic cancer with at least one of the following:

- One first or second degree blood relative with
  - Male breast cancer, or
  - Breast cancer at  $\leq 50$ , or
  - Two primary breast cancers
- Two first or second degree blood relatives on the same side of the family with breast or pancreatic cancer at any age
- Two first or second degree blood relatives with pancreatic cancer at any age
- Family history includes one of the following:
  - Individual has a first or second degree blood relative who meets any of the above PALB2 criteria
  - At risk individual from a family with a known familial PALB2 mutation

## von Hippel-Lindau

VHL 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 mutation
- 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

## CPT Codes

The following codes are associated with the guidelines in this document. This list is not all inclusive.

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

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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
- 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
- 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

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- 81323 PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion 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

## 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 mutations identified within a tumor are acquired, there are several cancer predisposition syndromes caused by inherited germline mutations. 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,*

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*Hereditary breast and ovarian cancer syndrome, 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.*

## **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 (ARUP 2011; Bellcross et al. 2011; Plon et al. 2011). 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).

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 mutation 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 multigene 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 include 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 mutation**

As tumor testing, especially broad molecular profiling becomes more common, it is expected that there will be an increase in the number of somatic mutations identified in genes associated with hereditary cancer syndromes. In most cases, this is associated with a risk that a germline mutation will be identified, but with certain cancer types and genes, the likelihood of an underlying germline mutation 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 mutations identified in endometrial cancer, despite the fact that germline mutations in APC are not associated with an increased risk of endometrial cancer.

Several studies have shown that the prevalence of pathogenic germline mutations among those in whom somatic mutations 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 mutations 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 mutations 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 mutations (Jain et al. 2016). For instance, TP53 mutations 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 mutation. 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.

### **CHEK2**

Several genes have been implicated in non-BRCA1/BRCA2 hereditary breast cancer families including CHEK2. CHEK2 mutations have been identified in up to 2% of breast cancer patients with a strong

family history of breast/ovarian cancer who had previously tested negative for mutations in BRCA1/BRCA2 (Li et al. 2016). The greatest breadth of research related to CHEK2 has focused on the c.1100delC variant which appears to confer an approximately two- to threefold increase in breast cancer risk in women and a tenfold increase in risk in men (CHEK2 Breast Cancer Case-Control Consortium 2004). CHEK2 mutations are associated with a relatively low breast cancer penetrance. One study estimates a cumulative risk to age 80 for the development of ER-positive invasive breast cancer of 20% and only 3% for ER-negative invasive breast cancer in female carriers of the CHEK2 1100delC variant (Schmidt et al. 2016). Some evidence suggests a stronger association among families with early-onset breast cancer than those with later-onset breast cancer. Kapoor et al. (2015) performed a retrospective review of 337 patients meeting NCCN Guidelines® for BRCA1/2 mutation testing, 25 of whom had non-BRCA mutations with CHEK2 variants accounting for 15% of the subgroup.

Breast MRI is recommended for all female CHEK2 mutation carriers (NCCN® v2.2019) due to the estimated lifetime risk of breast cancer exceeding 20%, and chemoprevention may be considered; however, NCCN® notes there is insufficient evidence for risk-reducing mastectomy. CHEK2 mutations have also been implicated in association with colorectal cancer (Ma et al. 2014), male breast cancer (Wasielewski et al. 2009), among other cancer types (Cybulski et al. 2004); however, no standard management recommendations exist for other cancer types at this time. Additionally, no standard published guidelines with testing criteria exist to guide the appropriate use of CHEK2 genetic testing.

## **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 parasympathetic 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 hyper secrete 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; Lenders et al. 2014).

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. Recent research has also indicated that those with noradrenergic tumors are at a higher risk for mutations in a wide variety of genes including MDH2 and HIF2A (Gupta 2017). In certain scenarios, testing with a targeted panel is reasonable.

Recently, germline FH mutations have been identified in a small subset of patients presenting with pheochromocytomas and paragangliomas (Castro-Vega et al. 2014; Clark et al. 2014); however, at this time there is not enough evidence to support broad FH testing for patients with PCC/PGL.

## PALB2

PALB2 (Partner and Localizer of BRCA2) interacts with the BRCA2 protein and is also involved in DNA repair. Homozygous mutations in PALB2 are additionally associated with Fanconi Anemia.

Among 1,144 familial breast cancer patients not selected by ancestry, 3.4% were identified to carry PALB2 mutations (Casadei et al. 2011). The cumulative breast cancer risk among women who have a germline mutation in PALB2 was previously estimated to be increased by two-fold (Tischkowitz et al. 2007). A higher breast cancer risk has been estimated for the c.1592delT Finnish founder mutation (OR3.94, 95% CI 1.5-12.1) (Erkko et al. 2013). Founder mutations have also been identified in a Polish population (c.509\_510delGA) and an Australian population (c.3113G>A) (Dansonka-Mieszkowska A et al. 2010; Teo ZL et al. 2013). A recent study by Antoniou et al. (2014) included 362 members of 154 families who had deleterious PALB2 mutations to determine age-specific breast-cancer risks for mutation carriers. The following risks were elucidated:

- The risk of breast cancer for female PALB2 mutation carriers, as compared with the general population, was eight to nine times as high among those younger than 40 years of age, six to eight times as high among those 40 to 60 years of age, and five times as high among those older than 60 years of age
- The estimated cumulative risk of breast cancer among female mutation carriers was 14% (95% confidence interval [CI], 9 to 20) by 50 years of age and 35% (95% CI, 26 to 46) by 70 years of age. Breast-cancer risk was also significantly influenced by birth cohort ( $P<0.001$ ) and by other familial factors ( $P=0.04$ )
- The absolute breast-cancer risk for PALB2 female mutation carriers by 70 years of age ranged from 33% (95% CI, 25 to 44) for those with no family history of breast cancer to 58% (95% CI, 50 to 66) for those with two or more first-degree relatives with breast cancer by 50 years of age

Male breast cancer has also been observed in PALB2 mutation-positive breast cancer families (Casadei et al. 2011; Ding et al. 2011).

Large scale exome analysis of both germline and somatic alterations in cases of ovarian cancer, pancreatic cancer and melanoma have identified an increased incidence of PALB2 mutations, however, specific risks for such cancers is not yet known and the NCCN® (v2.2019) currently categorizes PALB2 as having insufficient evidence for ovarian cancer, pancreatic or melanoma intervention at this time.

## Prostate Cancer

Most cases of prostate cancer occur sporadically with increased risks associated with advancing age and race. However, prostate cancer may also occur as a feature of well-described hereditary cancer syndromes such as hereditary breast and ovarian cancer (HBOC) caused by a BRCA1/BRCA2 mutation, mismatch repair gene defects or in the context of concerning family clusters of prostate cancer which do not fit a well-described cancer syndrome.

These latter cases may be classified as Hereditary Prostate Cancer (HPC) or Familial Prostate Cancer (FPC). HPC is generally defined as nuclear families with 3 cases of prostate cancer, families with prostate cancer in each of three consecutive generations, and/or families with at least two men diagnosed with prostate cancer before age 55 years (Madersbacher et al. 2011). FPC is typically defined as familial aggregation of prostate cancer not meeting HPC criteria (Alberti 2010). Overall, 5-

10% of prostate cancers have been described with clear Mendelian inheritance/HPC (Alberti 2010; Madersbacher et al. 2011), while up to about 25% of cases have been described as FPC (Alberti 2010).

The genetics behind HPC and FPC are not well understood, though genome-wide association studies (GWAS) have identified several molecular targets conferring minor increase in relative risk. These variants are associated with minimal increased risk in isolation, but may be associated with greater cumulative risk when observed in aggregate. Family history is also well-described as a major risk factor for increased prostate cancer risk (Alberti 2010; Madersbacher et al. 2011). Genetic risk factors are thought to contribute to 57% of interindividual variation in prostate cancer risk overall (Pritchard et al. 2016).

Pritchard et al. (2016) evaluated several case series which cumulatively included 692 men with known metastatic prostate cancer. Twenty DNA-repair genes were evaluated across all case studies and a known or presumed deleterious germline mutation was identified in 11.8% of these individuals. Mutations were identified in the following genes: BRCA2 (5%), ATM (2%), CHEK2 (2%), BRCA1 (1%), RAD51D (0.4%), PALB2 (0.4%), ATR (0.3%), and NBN, PMS2, GEN1, MSH2, MSH6, RAD51C, MRE11A, BRIP1, or FAM175A. The authors note the significance of this overall mutation frequency in comparison to a previous study of 499 men with localized prostate cancer (Cancer Genome Atlas Prostate Cancer Study), which yielded a 4.6% mutation rate. They also compared their results to the Exome Aggregation Consortium data, which identified a DNA-repair gene mutation in 2.7% of >53,000 total participants without a known cancer diagnosis.

The NCCN® Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Prostate Cancer (version 4.2018) includes germline testing recommendations for individuals with stage III (NCCN® high-risk and very-high-risk categories), regional and metastatic prostate cancer that includes BRCA1/2, ATM, PALB2 and FANCA given the relatively high frequency of germline mutations in this population. At this time, the clinical utility of germline testing for FANCA is unclear, however there are document management changes for BRCA1/2, ATM and PALB2. In addition, testing for mutations in high-risk individuals may allow for additional testing and monitoring in family members.

Family history information was available to some extent for 72 of the 82 men with presumed pathogenic mutations in the Pritchard et al. (2016) study; however, only the presence or absence of cancer was reported in first-degree relatives or cancer beyond first-degree relatives. The specific types of cancer were only known in an even smaller subset of participants. While this publication did not report on whether participants met best practice testing guidelines for the gene identified, supplemental materials allow for some investigation of this question. For those with confirmed pathogenic mutations in BRCA1/2 and some reported family history, nine of the 82 men (~11%) met NCCN Guidelines® testing criteria at that time, 11 of 82 (13.4%) had reported personal and family history which may have met NCCN Guidelines® testing criteria, and 13 of 82 men (15.9%) clearly did not meet NCCN Guidelines® testing criteria at that time.

## **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. Mutations 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 mutations.

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 Committee on Practice Bulletins--Gynecology; ACOG Committee on Genetics; Society of Gynecologic Oncologists. ACOG Practice Bulletin No. 182: Hereditary breast and ovarian cancer syndrome. *Obstet Gynecol.* 2017 Sep;130(3):657-659. PubMed PMID: 28832475.

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- Neuroendocrine Tumors and Adrenal Tumors (Version 2.2018). Accessed August 29, 2018.
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The NCCN Guidelines® are a work in progress that may be refined as often as new significant data becomes available.

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# Revision History

## Medical Advisory Board Review:

v1.2019 11/07/2018: Reviewed

v1.2018 03/31/2018: Reviewed

## Clinical Steering Committee Review:

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
v1.2019	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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