

Clinical Appropriateness Guidelines

Genetic Testing for Heredity 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 Somatic Tumor Testing Guidelines).

Appropriate Use Criteria

Genetic testing for hereditary cancer susceptibility is medically necessary when all of the following criteria are met:

- Genetic testing results will impact medical management
- National Comprehensive Cancer Network Guidelines™ (NCCN GUIDELINES®) include category 1, 2A, or 2B 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 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 this guideline 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, 2A, or 2B and/or other published management recommendations for all genes included in the panel

NCCN® Criteria¹

Genetic testing for the following syndromes is medically necessary when an individual meets the testing criteria outlined in the relevant NCCN GUIDELINES® (Gastric Cancer, v4.2017; Genetic/Familial

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High-Risk Assessment: Colorectal, v2.2017; Genetic/Familial High-Risk Assessment: Breast and Ovarian, v2.2017; Neuroendocrine Tumors, v3.2017):

- 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 <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
 - 1 first or second degree relative with breast cancer at any age or male breast cancer
 - an unknown or limited family history, defined as fewer than 2 first or second degree relatives in either lineage surviving beyond 60

- Personal history of female breast cancer diagnosed at any age with one of the following:
 - 1 first or second degree blood relative with breast cancer <50 or male breast cancer at any age
 - 2 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
- No personal history of breast cancer with 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.

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 at or under age 50 with at least one of the following:
 - additional primary breast cancer at any age
 - 1 first or second degree blood relative with
 - pancreatic cancer, or
 - breast cancer at ≤ 50 , or
 - male breast cancer, or
 - two primary breast cancers at any age
 - 2 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 with two primary breast cancers with one of the following:
 - 1 first or second degree blood relative with
 - pancreatic cancer, or
 - male breast cancer, or
 - breast cancer at ≤ 50 , or
 - two primary breast cancers
 - 2 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:
 - 2 first or second degree blood relatives on the same side of the family with at least one of the following:
 - male breast cancer, or
 - female breast cancer diagnosed < 50 , or
 - two primary breast cancers, or
 - pancreatic cancer
 - 3 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:
 - 1 first or second degree blood relative with
 - pancreatic cancer, or
 - male breast cancer, or
 - breast cancer < 50 , or
 - two primary breast cancers at any age
 - 2 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:
 - 1 first or second degree blood relative with
 - male breast cancer, or
 - breast cancer at < 50 , or
 - two primary breast cancers

- 2 first or second degree blood relatives on the same side of the family with breast or pancreatic cancer at any age
- 2 first or second degree blood relatives with pancreatic cancer at any age
- No personal history of breast or pancreatic cancer with 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.

81201	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
81202	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
81203	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants
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 14 genes, including ATM, BRCA1, BRCA2, BRIP1, CDH1, MLH1, MSH2, MSH6, NBN, PALB2, PTEN, RAD51C, STK11, and TP53

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- 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 adenomatosis 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 adenomatosis 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
- 81162 BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis
- 81211 BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in BRCA1 (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon
- 81212 BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
- 81213 BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; uncommon duplication/deletion variants
- 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

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- 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 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
- 81318 PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
- 81319 PMS2 (postmeiotic 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

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.

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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 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.

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 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 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® v2.2017) 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 2014), male breast cancer (Wasielewski 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 parasymphathetic paragangliomas are located predominantly in the skull base, neck, and upper mediastinum; approximately 95% of such tumors are nonsecretory. 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 2011, Lenders 2014).

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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 2014; Clark 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 1144 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 (or 3.94, 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 2010, and Teo ZL 201). 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® (v2.2017) currently categorizes PALB2 as having insufficient evidence for ovarian cancer, pancreatic or melanoma intervention at this time.

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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/presymptomatic relatives, including at-risk children (Nielsen et al., 2016).

Professional Society Guidelines

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These Guidelines are a work in progress that may be refined as often as new significant data becomes available.

The NCCN Guidelines® are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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Revision History

Clinical Steering Committee Review:

v3.2017 11/01/2017: Approved

v2.2017 05/03/2017: Approved

v1.2017 01/25/2017: Approved

Revisions:

Version	Date	Editor	Description
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

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