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 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 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 and 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 (NCCN Guideline®), (Gastric Cancer, v2.2020; Genetic/Familial High-Risk Assessment: Colorectal, v1.2020; Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic v1.2021; Neuroendocrine and Adrenal Tumors, v2.2020):

- 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

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

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 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
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 adenomatosis 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)

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 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.*

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 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 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 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 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 Leeuwaarde 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 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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NCCN® Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © 2019 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN® website: http://www.nccn.org/index.asp.*

- Gastric Cancer. (Version 2.2020). Accessed July 24, 2020.
- Genetic/Familial High-Risk Assessment: Colorectal (Version 1.2020). Accessed July 24, 2020.
- Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic (Version 1.2021). Accessed September 9, 2020.
- Neuroendocrine Tumors and Adrenal Tumors (Version 2.2020). Accessed July 24, 2020.

*Referenced with permission from the NCCN® Clinical Practice Guidelines in Oncology (NCCN Guidelines®) available at: http://www.nccn.org. Accessed September 9, 2020 ©National Comprehensive Cancer Network, 2020. To view the most recent and complete version of the NCCN Guidelines®, go online to www.nccn.org.

The NCCN 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

Medical Advisory Board Review:

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

Clinical Steering Committee Review:

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
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 criteria was updated. CPT codes, background, Professional Society/NCCN® guidelines and references were updated.
	2/5/2020	Carrie Langbo, MS, CGC	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.
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	Michele Gabree, MS, CGC	Semi-annual review. No criteria changes. Text clarification made for prostate cancer germline testing. Updated references.
	07/25/2019	Carrie Langbo, MS, CGC	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.
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 (≤) 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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