

Clinical Appropriateness Guidelines

Genetic Testing for Hereditary Cancer Susceptibility

EFFECTIVE MARCH 3, 2020

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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) or reproductive testing for hereditary cancer syndromes (see Clinical Appropriateness Guidelines for Reproductive Carrier Screening and Prenatal Diagnosis). 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

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- 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.)

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 susceptibility 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, MSH3, 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, v4.2019; Genetic/Familial High-Risk Assessment: Colorectal, v3.2019; Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic v1.2020; Neuroendocrine and Adrenal Tumors, v1.2019):

- 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
 - One diagnosis of breast cancer at any age in a close blood relative (male or female)
 - An unknown or limited family history, defined as fewer than two close blood relatives (female) in either lineage surviving beyond 60
- Personal history of female breast cancer diagnosed at any age with one of the following:
 - One diagnosis of breast cancer ≤ 50 or male breast cancer at any age in a close blood relative
 - Two diagnoses of breast cancer at any age in one or two close blood relative(s) on the same side of the family
- Personal history of male breast cancer at any age with at least one diagnosis of breast cancer at any age in a close blood relative
- Family history includes either of the following:
 - Individual has a close blood relative (male or female) who meets any of the above CHEK2 criteria
 - At risk individual from a family with a known familial P/LP variant in the CHEK2 gene

*Close blood relative is defined as a first or second degree blood relative.

**Please see Prostate Cancer section for additional criteria.

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.

Prostate Cancer

Genetic testing of BRCA1/2, ATM, PALB2, and CHEK2 is 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 ≤ 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
 - Personal history of pancreatic cancer
 - One close blood relative with
 - Pancreatic cancer, or
 - Breast cancer at ≤ 50 , or
 - Male breast cancer, or
 - Two primary breast cancers at any age
 - Two diagnoses of breast cancer at any age in one or two close blood relative(s) on the same side of the family
 - An unknown or limited family history (i.e., fewer than two close blood relatives (female) 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 close blood relative with
 - Pancreatic cancer, or
 - Male breast cancer, or
 - Breast cancer at ≤ 50 , or
 - Two primary breast cancers
 - Two diagnoses of breast cancer at any age in one or two close blood relative(s) on the same side of the family
- Personal history of female breast cancer diagnosed at any age with at least one of the following:
 - Two close 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 diagnoses of either breast and/or pancreatic cancer at any age in a close blood relative(s)
- Personal history of male breast cancer at any age with at least one of the following:
 - One close blood relative with
 - Pancreatic cancer, or
 - Male breast cancer, or
 - Breast cancer ≤ 50 , or
 - Two primary breast cancers at any age
 - Two diagnoses of breast cancer at any age in one or more close blood relative(s) on the same side of the family
- Personal history of pancreatic cancer with at least one of the following:
 - Personal history of breast cancer at ≤ 50
 - One close blood relative with
 - Male breast cancer, or
 - Breast cancer at ≤ 50 , or
 - Two primary breast cancers
 - Two diagnoses of either breast and/or pancreatic cancer at any age in one or more close blood relative(s) on the same side of the family
- Family history includes one of the following:
 - Individual has a close blood relative who meets any of the above PALB2 criteria
 - At risk individual from a family with a known familial P/LP variant in the PALB2 gene

*Close blood relative is defined as a first or second degree blood relative.

**Please see Prostate Cancer section for additional criteria.

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

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- 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.

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

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- 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
- 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

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- 81437 Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); genomic sequence analysis panel, must include sequencing of at least 6 genes, including MAX, SDHB, SDHC, SDHD, TMEM127, and VHL
- 81438 Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL
- 0129U Hereditary breast cancer–related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53)

Codes that do not meet medical necessity criteria:

- 0101U Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatous polyposis), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated (15 genes [sequencing and deletion/duplication], EPCAM and GREM1 [deletion/duplication only])
- 0102U Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated (17 genes [sequencing and deletion/duplication])
- 0103U Hereditary ovarian cancer (eg, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated (24 genes [sequencing and deletion/duplication], EPCAM [deletion/duplication only])
- 0130U-
0138U +RNAInsight™ (Ambry Genetics®)
- 0157U APC (APC regulator of WNT signaling pathway) (eg, familial adenomatous polyposis [FAP]) mRNA sequence analysis (List separately in addition to code for primary procedure) (Use 0157U in conjunction with 81201)
- 0158U MLH1 (mutL homolog 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure) (Use 0158U in conjunction with 81292)
- 0159U MSH2 (mutS homolog 2) (eg, hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure) (Use 0159U in conjunction with 81295)

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- 0160U MSH6 (mutS homolog 6) (eg, hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure) (Use 0160U in conjunction with 81298)
- 0161U PMS2 (PMS1 homolog 2, mismatch repair system component) (eg, hereditary nonpolyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure) (Use 0161U in conjunction with 81317)
- 0162U Hereditary colon cancer (Lynch syndrome), targeted mRNA sequence analysis panel (MLH1, MSH2, MSH6, PMS2) (List separately in addition to code for primary procedure) (Use 0162U in conjunction with 81292, 81295, 81298, 81317, 81435)
- 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 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

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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

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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.

CHEK2

Several genes have been implicated in non-BRCA1/BRCA2 hereditary breast cancer families including CHEK2. CHEK2 P/LP variants 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 P/LP variants 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 P/LP variants 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 P/LP variant testing, 25 of whom had non-BRCA variants with CHEK2 variants accounting for 15% of the subgroup.

Breast MRI is recommended for all female CHEK2 P/LP variant carriers (NCCN® v1.2020) 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 P/LP variants 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 except for colorectal cancer. NCCN recommends colonoscopy screening every five years, beginning at age 40 or ten years prior to the age of colon cancer diagnosis of an affected first degree relative, whichever comes first.

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. Recent 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.

Recently, germline FH P/LP variants 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 P/LP variants 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 P/LP variants (Casadei et al. 2011). The cumulative breast cancer risk among women who have a germline P/LP variant 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 pathogenic variant (OR 3.94, 95% CI 1.5-12.1) (Erkko et al. 2013). Founder P/LP variants 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 P/LP variants to determine age-specific breast-cancer risks for P/LP variant carriers. The following risks were elucidated:

- The risk of breast cancer for female PALB2 P/LP variant 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 P/LP variant 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 P/LP variant 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 P/LP variant-positive breast cancer families (Casadei et al. 2011; Ding et al. 2011). Given the elevated breast cancer risk, NCCN® (v1.2020) recommends consideration of annual breast MRI beginning at age 30 for all female PALB2 P/LP variant carriers. Additionally, chemoprevention and risk-reducing mastectomy can be discussed as other options for managing the breast cancer risk (NCCN® v1.2020).

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 P/LP variants, however, specific risks for these cancers are not well-established. While NCCN® (v1.2020) currently categorizes PALB2 as having insufficient evidence for ovarian cancer or melanoma intervention, they do recommend consideration of screening for pancreatic cancer. For PALB2 P/LP variant carriers with at least a first or second degree relative affected with exocrine pancreatic cancer, NCCN® recommends initiation of annual pancreatic cancer screening at age 50 (or 10 years younger than the earliest age of diagnosis in the family). This recommendation is similar to the recent guidelines from the International Cancer of the Pancreas Screening Consortium (CAPS) (Goggins et al. 2020).

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 P/LP variants, 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 P/LP variant was identified in 11.8% of these individuals. P/LP variants 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 P/LP variant 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% P/LP variant rate. They also compared their results to the Exome Aggregation Consortium data, which identified a DNA-repair gene variant 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 4.2019) includes germline testing recommendations for individuals with stage III (NCCN® high-risk and very-high-risk categories), regional or metastatic prostate cancer that includes BRCA1/2, ATM, CHEK2, and PALB2 given the relatively high frequency of germline P/LP variants in this population. In addition, there are documented management changes for those who are found to be positive for BRCA1/2, ATM, CHEK2, PALB2 or RAD51D. Testing for P/LP variants in high-risk individuals may allow for additional testing and monitoring in family members. NCCN Guidelines® (v4.2019) also include MLH1, MSH2, MSH6, and PMS2 (for Lynch syndrome) for testing. However, there are currently no medical management recommendations for these genes (NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Colorectal, v.3.2019). Therefore, these genes do not meet AIM Guideline criteria.

Family history information was available to some extent for 72 of the 82 men with presumed pathogenic variants 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 variants 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. P/LP variants in the VHL gene are inherited in an autosomal dominant manner. It is estimated that 80% of individuals with VHL inherited it from an affected parent, and approximately 20% are due to new or de novo P/LP variants (van Leeuwen et al. 2019).

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

Professional Society Guidelines

American College of Obstetricians and Gynecologists; ACOG 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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Revision History

Medical Advisory Board Review:

v1.2020 11/04/2019: Approved

v2.2019 05/23/2019: No Criteria Changes

v1.2019 11/07/2018: Reviewed

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v1.2018 03/31/2018: Reviewed

Clinical Steering Committee Review:

v1.2020 10/11/2019: Approved

v3.2019 12/09/2019: Approved

v2.2019 05/20/2019: Approved

v1.2019 10/03/2018: Approved

v1.2018 02/28/2018: Approved

v3.2017 11/01/2017: Approved

v2.2017 05/03/2017: Approved

v1.2017 01/25/2017: Approved

Revisions:

Version	Date	Editor	Description
v1.2020	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.

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	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 (\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

Primary Author: Marie Schuetzle, MS, CGC

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