

## Clinical Appropriateness Guidelines

# Genetic Testing for Hereditary Cancer Susceptibility



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# Scope

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

## Genetic Counseling Requirement

### **Genetic testing included in these guidelines is covered when:**

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

### Who:

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

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*\*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:

- Results are expected to lead to a change in 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
- An individual's personal and/or family history meets specific testing criteria suggestive of a hereditary cancer syndrome based on best practice 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:

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

After a somatic variant is identified in a solid tumor or hematologic malignancy, follow-up germline testing for that variant is medically necessary when the following criteria are met:

- There are NCCN Guidelines<sup>®</sup> category 1 or 2A and/or other published management recommendations specific to germline pathogenic/likely pathogenic (P/LP) variants in the requested gene
- There is high clinical suspicion for the variant to be germline based on patient and/or family history OR characteristics of the variant itself (e.g., high allele frequency in tumor sample, well-described founder P/LP variants, concordance between gene and associated tumor type)

### **National Comprehensive Cancer Network<sup>®</sup> (NCCN<sup>®</sup>) Criteria**

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

- Hereditary Colorectal Cancer Syndromes
  - Hereditary Colorectal Cancer syndromes include: Lynch syndrome, Familial adenomatous polyposis (FAP)/Attenuated familial adenomatous polyposis (AFAP), MYH associated polyposis, Juvenile polyposis syndrome, Peutz-Jeghers syndrome, Serrated Polyposis Syndrome

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- For the purpose of evaluating criteria, Lynch syndrome related cancers include: colorectal, endometrial, keratoacanthoma, stomach, ovarian, small bowel, urothelial, sebaceous adenoma or carcinoma, hepatobiliary, pancreas, and brain cancer
  - Testing is targeted to the genes listed in NCCN<sup>®</sup> Genetic/Familial High-Risk Colorectal Cancer, v1.2021
- Hereditary Breast and Ovarian Cancer Syndromes
  - Hereditary Breast and Ovarian Cancer syndromes include: Hereditary Breast and Ovarian Cancer syndrome, Cowden syndrome/PTEN Hamartoma tumor syndrome, Li Fraumeni syndrome, and other breast/ovarian cancer susceptibility syndromes
    - For the purpose of evaluating criteria, Hereditary Breast and Ovarian Cancer syndromes related cancers include: breast, ovarian, pancreatic and prostate cancer.
  - Testing is targeted to the susceptibility genes (*high and moderate penetrant genes*) listed in NCCN<sup>®</sup> Genetic/Familial High-Risk Breast, Ovarian and Pancreatic, v1.2023

## 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   |

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- 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

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- 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

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- 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

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paraganglioma); duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL

0129U Hereditary breast cancer–related disorders (eg, hereditary breast cancer, (BRCAplus®) hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53)

Considered not medically necessary;

*(Proprietary tests that do not meet criteria are considered not medically necessary when submitted with their specific assigned code listed below or any less specific coding.)*

0130U-01 +RNAInsight™ (Ambry Genetics®)  
38U

0157U APC (APC regulator of WNT signaling pathway) (eg, familial adenomatosis (CustomNext polyposis [FAP]) mRNA sequence analysis (List separately in addition to + RNAInsight™: code for primary procedure) (Use 0157U in conjunction with 81201) APC)

0158U MLH1 (mutL homolog 1) (eg, hereditary non-polyposis colorectal cancer, (CustomNext Lynch syndrome) mRNA sequence analysis (List separately in addition to + RNAInsight™: code for primary procedure) (Use 0158U in conjunction with 81292) MLH1)

0159U MSH2 (mutS homolog 2) (eg, hereditary colon cancer, Lynch syndrome) (CustomNext mRNA sequence analysis (List separately in addition to code for primary + RNAInsight™: procedure) (Use 0159U in conjunction with 81295) MSH2)

0160U MSH6 (mutS homolog 6) (eg, hereditary colon cancer, Lynch syndrome) (CustomNext mRNA sequence analysis (List separately in addition to code for primary + RNAInsight™: procedure) (Use 0160U in conjunction with 81298) MSH6)

0161U PMS2 (PMS1 homolog 2, mismatch repair system component) (eg, (CustomNext hereditary nonpolyposis colorectal cancer, Lynch syndrome) mRNA + RNAInsight™: sequence analysis (List separately in addition to code for primary PMS2) procedure) (Use 0161U in conjunction with 81317)

0162U Hereditary colon cancer (Lynch syndrome), targeted mRNA sequence (CustomNext analysis panel (MLH1, MSH2, MSH6, PMS2) (List separately in addition to +

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RNAInsight™: code for primary procedure) (Use 0162U in conjunction with 81292, 81295, Lynch (MLH1, MSH2, MSH6, PMS2) 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  
(Genomic Unity® PTEN Analysis)

ANY Myriad myRisk® (Myriad Genetics, Inc.)

ANY CancerNext® (Ambry Genetics®)

ANY Comprehensive Common Cancer Panel (GeneDx)

ANY Invitae Multi-Cancer Panel (Invitae Corporation)

ANY Invitae Common Hereditary Cancers Panel (Invitae Corporation)

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## Background

Cancer is caused by 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.

Next-generation sequencing technologies allow testing of multiple concurrent genes known or suspected to be associated with hereditary risk for developing cancer. It is prudent to

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understand the validity of gene/disease associations for genes included on multi-gene panels, as the clinical utility of gene sequencing decreases with decreasing evidence for disease (Bean et al. 2019). In addition, many current panels have a higher likelihood of returning a variant of uncertain significance (VUS) than a P/LP variant for any given patient (Samadder et al. 2020).

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

## **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. 2020). 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. 2020).

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

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

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

The American Society of Clinical Oncologists (ASCO) (Robson et al. 2015) additionally recognizes that multi-gene testing for hereditary cancer susceptibility is currently challenged by uncertainties and areas of needed study, and thus recommend that this testing is ideally handled by providers who are well educated on the complex nature of this genetic testing. Additional note is made that evidence has suggested that overinterpretation of variants identified in these panels by non-expert providers may harm patient care, such as inappropriate medical interventions and psychological stress. Thus, since 1996 ASCO has recommended that pre-test counseling for hereditary predisposition testing includes, at minimum: details on the purpose of testing, potential outcomes, implications for the patient and their family members, risks associated with the genes being tested, costs associated, psychological implications, risks and protections for genetic discrimination, confidentiality issues related to genetic testing, research use of samples, alternate options to testing, utility of medical surveillance and prevention, importance of sharing results with at risk relatives, follow up planning for results, rate of variants of uncertain significance, as well as contrast of

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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 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 that specific 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 (Jain et al. 2016). In a recent statement from the American College of Medical Genetics, it is affirmed that there is insufficient evidence to inform “best practices” for reporting presumed germline pathogenic variants (PGPVs) when tumor testing is performed (Li et al. 2020). It is acknowledged that evidence is emerging in support of an analysis pipeline for tumor testing that is designed to identify PGPVs. However, it is also noted that tumor-normal paired testing is not a replacement for dedicated germline genetic testing given that not all PGPVs will be identified with this approach (Li et al. 2020).

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; Bekos et al. 2021). 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 et al. 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; Mandelker et al. 2019). 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 the likelihood of a germline

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origin should be considered when determining medical necessity of germline testing for these actionable genes.

# Professional Society Guidelines

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

ACOG Committee Opinion No. 793. Hereditary Cancer Syndromes and Risk Assessment. *Reaffirmed 2020.*

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

ACOG Committee Opinion No. 816. Consumer Testing for Disease Risk.

*Obstet Gynecol. 2021 Jan 1;137(1): e1-e6. PubMed PMID: 33399428.*

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

ACMG Points to Consider Statement. DNA-Based Screening and Population Health.

*Murray M, Giovanni M, Doyle D, et al. Genet Med. 2021 Jun;23(6):989-995. PubMed PMID: 33727704.*

ACMG Points to Consider Statement. Incidental Detection of Acquired Variants in Germline Genetic and Genomic Testing.

*Chao EC, Astbury C, Deignan JL, et al. Genet Med. 2021 Apr 16. PubMed PMID: 33864022.*

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

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

ACMG Points to Consider Statement. Reporting of Germline Variation in Patients Undergoing Tumor Testing.

*Li M.M., Chao E., Esplin E.D. et al. Genet Med. 2020 Apr 23. PubMed PMID: 32321997.*

ACMG Practice Resource. Management of Individuals with Germline Variants in PALB2.

*Tischkowitz M, Balmana J, Goulkes W, et al. Genet Med. 2021 May 11. PubMed PMID: 33976419.*

ACMG Technical Standard. Genetic Testing for Inherited Colorectal Cancer and Polyposis, 2021 revision.

*Mao R, Krautscheid P, Graham RP, et al.; ACMG Laboratory Quality Assurance Committee. Genet Med. 2021 Jun 17. PubMed PMID: 34140662.*

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

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

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

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Adjuvant PARP Inhibitors in Patients with High-Risk Early-Stage HER2-Negative Breast Cancer and Germline BRCA Mutations: ASCO Hereditary Breast Cancer Guideline Rapid Recommendation Update.

*Tung N, Zakalik D, Somerfield M. J Clin Oncol. 2021 Sep 10;39(26):2959-2961. PubMed PMID: 34343058.*

### **Endocrine Society**

Clinical Practice Guideline. Pheochromocytoma and Paraganglioma

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

### **European Society of Medical Oncology**

Germline-Focused Analysis of Tumour-Only Sequencing: Recommendations from the ESMO Precision Medicine Working Group.

*Mandelker D, Donoghue M, Talukdar S, et al. Ann Oncol. 2019 Aug 1;30(8):1221-1231. Erratum in: Ann Oncol. 2021 Jun 2. PubMed PMID: 31050713.*

### **International Gastric Cancer Linkage Consortium (IGCLC)**

Hereditary Diffuse Gastric Cancer: Updated Clinical Practice Guidelines.

*Blair VR, McLeod M, Carneiro F, et al. Lancet Oncol. 2020 Aug;21(8): e386-e397. PubMed PMID: 32758476*

### **Joint Statements**

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

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

### **NCCN® Clinical Practice Guidelines in Oncology (NCCN Guidelines®)**

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- Genetic/Familial High-Risk Assessment: Colorectal (Version 1.2021). Accessed March 17, 2022.
- Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic (Version 1.2023). Accessed September 14, 2022.

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

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# Revision History

## Medical Advisory Board Review:

- v2.2022 03/17/2022: Approved
- v1.2022 09/20/2021: Approved
- v3.2021 09/07/2021: Approved
- v2.2021 03/12/2021: Approved
- v1.2021 11/13/2020: Approved
- v3.2020 11/13/2020: Approved
- v2.2020 05/08/2020: Reviewed
- v1.2020 11/04/2019: Approved
- v2.2019 05/23/2019: No Criteria Changes
- v1.2019 11/07/2018: Reviewed
- v1.2018 03/31/2018: Reviewed

## Clinical Steering Committee Review:

- v3.2022 09/14/2022: Approved
- v2.2022 02/14/2022: Approved
- v1.2022 08/23/2021: Approved

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v3.2021 09/07/2021: Approved  
v2.2021 02/22/2021: Approved  
v1.2021 10/13/2020: Approved  
v3.2020 10/13/2020: Approved  
v2.2020 04/06/2020: Approved  
v1.2020 10/11/2019: Approved  
v3.2019 12/09/2019: Approved  
v2.2019 05/20/2019: Approved  
v1.2019 10/03/2018: Approved  
v1.2018 02/28/2018: Approved  
v3.2017 11/01/2017: Approved  
v2.2017 05/03/2017: Approved  
v1.2017 01/25/2017: Approved

**Revisions:**

<b>Version</b>	<b>Date</b>	<b>Editor</b>	<b>Description</b>
v3.2022 GEN 02-1022.2a	09/14/2022	Eleanor Riggs, MS, CGC	Interim Update: NCCN Guidelines® Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (Version 1.2023) was updated.
v2.20222 GEN 02-0922.1	02/02/2022	Eleanor Riggs, MS, CGC	Semi-annual review. The NCCN Guideline® section was updated and the hereditary paraganglioma-pheochromocytoma (PGL/PCC) and von Hippel Lindau syndromes sections were removed. CPT codes, professional society guidelines, background and references were updated.
v1.2022 GEN 02-0322.1	8/16/2021	Eleanor Riggs, MS, CGC and Stefanie Finch, MS, CGC	Semi-annual review. The following sections were revised for clarity with no impact on coverage: Appropriate Use Criteria, Germline Testing Following Identification of a Somatic Variant, and PGL/PCC syndromes. NCCN Guideline® versions were updated. CPT codes,

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			professional society guidelines, background and references were updated.
v3.2021 GEN02-1121.1a	09/06/2021	Eleanor Riggs, MS, CGC	Interim Update: NCCN Guidelines® Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (Version 1.2022) was updated.
v2.2021 GEN02-0921.1	02/22/2021	Eleanor Riggs, MS, CGC	Semi-annual review. PGL/PCC and VHL criteria were clarified. NCCN Guidelines® Gastric Cancer v1.2021 was updated. Updated CPT codes, professional society guidelines, background and references.
v1.2021	9/11/2020	Stefanie Finch, MS, CGC and Eleanor Riggs, MS, CGC	Semi-annual review. Genetic counseling requirements were updated. Reformatted NCCN® criteria. Updated CPT codes, professional society guidelines, background and references.
v3.2020	10/9/2020	Eleanor Riggs, MS, CGC	Interim Update: NCCN Guidelines® Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (Version 1.2021) was updated. CPT codes were updated.
v2.2020	03/13/2020  07/24/2020	Eleanor Riggs, MS, CGC  Carrie Langbo, 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.  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

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

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			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,	Added PALB2 and CHEK2 criteria. Updated references.

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		MS, CGC	
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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