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Germline Genetic Testing for Hereditary Cancer Susceptibility Syndromes

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Scope

This evidence-based guideline addresses germline genetic testing for hereditary cancer susceptibility syndromes and germline genetic testing following identification of a somatic variant.

This guideline's coverage criteria delineate medically necessary clinical scenarios for molecular testing and may include specific situations when testing is considered never medically necessary. In general, molecular testing is considered never medically necessary when evidence demonstrating its ability to improve diagnosis, management, or clinical outcomes is lacking in peer-reviewed literature.

- Please refer to the Somatic Tumor Testing guideline for tissue-based and circulating tumor DNA (ctDNA) testing.
- Please refer to the General Genetic Testing guideline for the use of polygenic risk scores for cancer.

State Biomarker Legislation

Medical necessity determinations must also take into consideration controlling state coverage mandates that may supersede these guidelines when applicable. When state biomarker legislation requirements impact coverage decisions, this guideline will initially be applied to determine if criteria are met for approval. If an approval cannot be granted based on the criteria in this guideline, some or all of the following sources will be reviewed, as defined by applicable state legislation, to determine if test coverage is supported in a manner that is consistent with the state biomarker legislation requirements:

- Medicare National Coverage Determinations (NCDs)
- Medicare Local Coverage Determinations (LCDs)
- U.S. Food and Drug Administration (FDA) approved or cleared tests
- Tests indicated for an FDA-approved drug
- Nationally recognized clinical practice guidelines
- Consensus statements

Guideline Coverage Criteria

Germline Genetic Testing for Hereditary Cancer Susceptibility Syndromes

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

- Individual meets genetic testing criteria, e.g., National Comprehensive Cancer Network® (NCCN®) Clinical Practice Guidelines in Oncology (NCCN Guidelines®), American

Society of Clinical Oncology (ASCO), or other published clinical diagnostic criteria, for a hereditary cancer susceptibility syndrome (e.g., hereditary breast and ovarian cancer syndrome, Lynch syndrome, familial adenomatous polyposis, von Hippel-Lindau syndrome, Cowden syndrome, Li-Fraumeni syndrome)
- Results are expected to lead to a change in medical management
- There are NCCN Guidelines® category 1 or 2A, and/or other published management recommendations for the condition/syndrome-specific genes
- The individual is the most appropriate person to test or the most appropriate family member is unavailable for testing
- 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
- When the clinical presentation warrants testing of multiple genes, a multi-gene panel is reasonable when 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

*The testing methodology may target DNA and/or RNA.

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

Testing for genes lacking established clinical validity for hereditary cancer susceptibility syndromes (e.g., *FANCC*, *MRE11A*, *RAD50*, *RECQL4*, *RINT1*, *SLX4*, *XRCC2*, *GALNT12*, *SEMA4A*, *FAN1*, *ENG*, *XRCC4*, *BUB1*, *BUB3*, *PTPRJ*, *EXO1*, *PMS1, FOCAD*) is never medically necessary.

Germline Genetic 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® 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 variant allele frequency in tumor sample, well-described founder P/LP variants, concordance between gene and associated tumor type)

Key Terms and Definitions

Deoxyribonucleic acid (DNA) is a molecule that contains the genetic instructions for all living organisms and plays a crucial role in the development and susceptibility to diseases.
Founder pathogenic/likely pathogenic (P/LP) variant(s) are specific disease-causing variants that are found more frequently in certain populations.
Genes are segments of DNA that contain the instructions for specific traits, characteristics, or functions within an organism.
Genetic (molecular) testing examines a person's DNA or RNA to identify variations that can aid in the diagnosis of disease and/or provide valuable information about a person's risk of developing certain diseases.
Germline genetic testing involves examining the DNA found in every cell of the body derived from reproductive cells (eggs or sperm).
Hereditary cancer susceptibility is an increased risk of developing certain types of cancer due to an inherited genetic variant or variants, typically in genes that play critical roles in controlling cell growth, DNA repair, and tumor suppression.
Hereditary cancer syndromes are a group of genetic disorders characterized by an increased risk of developing certain types of cancers due to inheriting specific gene variants that disrupt normal regulation of cell growth.
Multi-gene panels simultaneously analyze multiple genes associated with a particular condition or a group of related conditions.
Pathogenic/likely pathogenic (P/LP) variant(s) are specific genetic changes that are known or highly likely to cause a particular genetic disorder, which can aid in diagnosis and/or guide treatment and management strategies.
Phenotype refers to the observable characteristics or features of a genetic disorder.
Ribonucleic acid (RNA) is a molecule that plays a crucial role in various cellular processes within living organisms, such as cell functioning and regulation.
Somatic variants are genetic changes that arise in a person's DNA during their lifetime. Somatic variants are not inherited or passed onto offspring. Many cancers are associated with the accumulation of somatic variants in specific genes that control cell growth and division.
Syndromic presentation refers to a combination of clinical features or symptoms that occur together as part of a recognizable pattern or syndrome.
Somatic tumor testing is a type of genetic testing that focuses on identifying genetic changes that occur spontaneously in tumor cells.
Variant allele frequency is a measure of how frequently a particular variant is detected in a tumor sample.
Variants of uncertain significance (VUS) are genetic changes detected during genetic testing that cannot be definitively classified as benign (harmless) or pathogenic (disease-causing). The impact on a person's health is not well understood based on scientific evidence available at the time of testing.

CPT® Codes

Medical necessity review of claims may include evaluation of the submitted codes. Laboratories must accurately represent their services using the most applicable and specific CPT code(s). Tier 1 molecular pathology procedure codes or Proprietary Laboratory Analyses (PLA) codes should be used when available for the specific test. Tier 2 molecular pathology procedure codes should only be used if the American Medical Association (AMA) has specifically assigned the performed test to such a code. Genomic sequencing procedures (GSP) codes (e.g., CPT codes 81410-81471) were developed by the AMA to represent multi-gene panels utilizing DNA or RNA analysis for specific clinical scenarios (e.g., carrier screening, tumor testing, etc.) and should be utilized when applicable.

Coding guidelines can be found in the AMA's CPT manual as well as the Centers for Medicare and Medicaid Services (CMS) National Correct Coding Initiative (NCCI) policy manuals. NCCI General Correct Coding Policy states that procedures should be reported with the most comprehensive CPT code describing the services performed and that the services described by a CPT code cannot be unbundled into multiple less specific codes. Additionally, GSP codes should be utilized when appropriate for the described test and should not be submitted along with other CPT codes that represent components of the GSP code.

Claims may not be approved if the submitted codes are not the most appropriate for the described procedure (i.e., as accurate and specific as available).

The following code(s) are medically necessary when coverage criteria are met. This list is not all inclusive.

Code	Full Description
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 adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
81202	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
81203	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis;

	duplication/deletion variants
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
81301	Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
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 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81318	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81319	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81321	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
81322	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene

	analysis; known familial variant
81323	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant
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, hereditary pancreatic cancer, hereditary prostate cancer); genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants
81435	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants
81437	Hereditary neuroendocrine tumor-related disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants
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])
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)
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

References

CPT Codes

AMA CPT® Professional 2024. American Medical Association

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Change Summary

Version	Review Date	Effective Date	Summary of Revisions
Created	CSC: 8/11/2022 PAB: 9/12/2022	November 2022	Not applicable
v1.2023	COOC: 2/15/2023 PAB: 3/16/2023	April 1, 2023	Semi-annual review. No criteria changes.
v2.2023	COOC: 8/16/2023	October 1, 2023	Semi-annual review. No criteria changes.

	PAB: 9/25/2023		
v1.2024	COOC: 2/14/2024 PAB: 3/25/2024	April 1, 2024	Semi-annual review. General coverage criteria were streamlined and updated to emphasize other professional societies in addition to NCCN may drive coverage decision-making. Clarifications were made to the CPT code section. References were updated.
v2.2024	COOC: 08/19/2024 PAB: 09/20/2024	October 1, 2024	Semi-annual review. FOCAD was added to the list of genes lacking established clinical validity for hereditary cancer susceptibility syndromes. References were updated.
v1.2025	COOC: 02/17/2025 PAB: 03/24/2025	July 3, 2025	Semi-annual review. No criteria changes. CPT codes and references were updated.