InformedDNA®
Genetics, Decoded.

Oncology Screening Tests

Policy Number: GT04.1

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Scope

This evidence-based guideline addresses genetic testing for the purpose of screening for cancer and includes symptomatic as well as population-based screening.

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.

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

Colorectal Cancer Screening

Cologuard (81528)/Cologuard Plus (0464U) is medically necessary when all of the following are met:

- individual is at an average risk* for colorectal cancer
- individual is ≥45 years of age with at least a 10 year life expectancy
- individual has either:
    - never had colorectal cancer screening
    - had prior negative screening and repeat screening is indicated per American Cancer Society Guidelines

**American Cancer Society Guidelines define those at average risk as not having any of the following: a personal history of colorectal cancer or certain types of polyps; a family history of colorectal cancer; a personal history of inflammatory bowel disease (ulcerative colitis or Crohn's disease); a confirmed or suspected hereditary colorectal cancer syndrome, such as familial adenomatous polyposis (FAP) or Lynch syndrome (hereditary non-polyposis colon cancer or HNPCC); a personal history of getting radiation to the abdomen (belly) or pelvic area to treat a prior cancer.*

Cutaneous Melanoma Screening

The use of gene expression classifier tests for indeterminate melanocytic lesions or indeterminate melanocytic neoplasms following histopathology is considered never medically necessary.

Indeterminate Thyroid Nodule Testing

Targeted multi-gene panels, Afirma® Genomic Sequence Classifier, ThyroSeq® v3, or ThyGeNEXT® / ThyraMIRv2™ are medically necessary for fine-needle aspiration samples of indeterminate thyroid nodules classified as The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) Category III atypia of undetermined significance or TBSRTC Category IV follicular neoplasm.

Population-Based Cancer Screening

The use of molecular testing for early cancer detection, e.g. multi-cancer early detection (MCED) testing, is never medically necessary.

Prostate Cancer Early Detection (Symptomatic Screening)

Gene expression classifiers for prostate cancer (symptomatic) screening are never medically necessary.

Key Terms and Definitions

Gene expression classifier testing is a molecular diagnostic technique that evaluates the activity levels of specific genes in a sample to classify or predict certain disease states or outcomes.
Genes are segments of DNA that contain the instructions for specific traits, characteristics, or functions within an organism.
Indeterminate thyroid nodules are growths (nodules) found in the thyroid gland with characteristics that make their diagnosis unclear based solely on a fine-needle aspiration (FNA) biopsy.
Multi-gene panels simultaneously analyze multiple genes associated with a particular condition or a group of related conditions.

Multi-cancer early detection (MCED) testing refers to non-invasive screening tests intended to detect cancer in individuals before they develop symptoms.
Population-based cancer screening is a systematic approach to screen a large segment of the population for cancer with the intention of identifying it at an early stage, e.g. MCED 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
81528	Oncology (colorectal) screening, quantitative real-time target and signal amplification of 10 DNA markers (KRAS mutations, promoter methylation of NDRG4 and BMP3) and fecal hemoglobin, utilizing stool, algorithm reported as a positive or negative result
81546	Oncology (thyroid), mRNA, gene expression analysis of 10,196 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (eg, benign or suspicious)
0018U	Oncology (thyroid), microRNA profiling by RT-PCR of 10 microRNA sequences, utilizing fine needle aspirate, algorithm reported as a positive or negative result for moderate to high risk of malignancy
0026U	Oncology (thyroid), DNA and mRNA of 112 genes, next-generation sequencing, fine needle aspirate of thyroid nodule, algorithmic analysis reported as a categorical result ("Positive, high probability of malignancy" or "Negative, low probability of malignancy")
0245U	Oncology (thyroid), mutation analysis of 10 genes and 37 RNA fusions and expression of 4 mRNA markers using next-generation sequencing, fine needle aspirate, report includes associated risk of malignancy expressed as a percentage

0464U	Oncology (colorectal) screening, quantitative real-time target and signal amplification, methylated DNA markers, including LASS4, LRRC4 and PPP2R5C, a reference marker ZDHHC1, and a protein marker (fecal hemoglobin), utilizing stool, algorithm reported as a positive or negative result

The following code(s) are considered never medically necessary. This list is not all inclusive.

Code	Full Description
81313	PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (eg, prostate cancer)
81551	Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (GSTP1, APC, RASSF1), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a likelihood of prostate cancer detection on repeat biopsy
0005U	Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score
0012M	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and XCR2), utilizing urine, algorithm reported as a risk score for having urothelial carcinoma
0089U	Oncology (melanoma), gene expression profiling by RTqPCR, PRAME and LINC00518, superficial collection using adhesive patch(es)
0090U	Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 23 genes (14 content and 9 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical result (ie, benign, intermediate, malignant)
0113U	Oncology (prostate), measurement of PCA3 and TMPRSS2-ERG in urine and PSA in serum following prostatic massage, by RNA amplification and fluorescence based detection, algorithm reported as risk score
0287U	Oncology (thyroid), DNA and mRNA, next generation sequencing analysis of 112 genes, fine needle aspirate or formalin fixed paraffin-embedded (FFPE) tissue, algorithmic prediction of cancer recurrence, reported as a categorical risk result (low, intermediate, high)
0339U	Oncology (prostate), mRNA expression profiling of HOXC6 and DLX1, reverse transcription polymerase chain reaction (RT-PCR), first-void urine following digital rectal examination, algorithm reported as probability of high-grade cancer
0433U	Oncology (prostate), 5 DNA regulatory markers by quantitative PCR, whole blood, algorithm, including prostate-specific antigen, reported as likelihood of cancer
0537U	Oncology (colorectal cancer), analysis of cell-free DNA for epigenomic patterns, next generation sequencing, >2500 differentially methylated regions (DMRs), plasma, algorithm reported as positive or negative

References

CPT Codes

AMA CPT® Professional 2024. American Medical Association

NCCI Policy Manual for Medicare Services. Available at:
https://www.cms.gov/Medicare/Coding/NationalCorrectCodInitEd. Accessed quarterly.

NCCI Policy Manual for Medicaid Services. Available at:
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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 PAB: 9/25/2023	October 1, 2023	Semi-annual review. ITN criteria were revised to remove the exclusion for follicular neoplasm - oncocytic follicular neoplasm (historically referred to as Hurthle cell predominance).
v1.2024	COOC: 2/14/2023 PAB: 3/25/2024	April 1, 2024	Semi-annual review. No criteria changes. Clarifications were made to the scope and CPT code sections. References were updated.
v2.2024	COOC: 08/19/2024 PAB: 09/20/2024	October 1, 2024	Semi-annual review. Cologuard Plus was added to the CRC screening section in anticipation of its commercial availability. CPT code and reference sections 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 updated.