InformedDNA®
Genetics, Decoded.

Oncology Screening Tests

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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

General Testing

Testing is medically necessary when all of the following criteria are met (*see additional indication-specific testing criteria listed below*):

- The test is customarily recognized as clinically reasonable:
    - Symptoms and presentation are consistent with the suspected condition
    - Results are expected to lead to a change in medical management
    - If testing guidelines exist, the clinical scenario falls within those recommendations
    - The clinical benefit of testing outweighs the potential risk of psychological or medical harm to the individual being tested
    - The clinical presentation warrants testing of multiple genes when a multi-gene panel is requested

- The test is customarily recognized as technically appropriate:
    - The test has established clinical validity/utility in the diagnosis and/or treatment of the suspected condition
    - The test is as targeted as possible for the clinical situation (e.g., familial pathogenic or likely pathogenic (P/LP) variant testing, common variants, genes related to phenotype)
    - The testing methodology[a] 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

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Criteria listed above are based primarily on the following resources. Publications issued after this guideline's effective date will be evaluated on an individual basis until criteria are incorporated in the next iteration of this guideline.

a. Bean LJH, Funke B, Carlston CM, et al. Diagnostic gene sequencing panels: from design to report-a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2020 Mar;22(3):453-461. doi: 10.1038/s41436-019-0666-z. Epub 2019 Nov 16. PMID: 31732716.
b. Holtzman NA. Promoting safe and effective genetic tests in the United States: work of the task force on genetic testing. Clin Chem. 1999 May;45(5):732-8. PMID: 10222375.
c. Matalon DR, Zepeda-Mendoza CJ, Aarabi M, et al. Electronic address: documents@acmg.net. Clinical, technical, and environmental biases influencing equitable access to clinical genetics/genomics testing: A points to consider statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2023 Jun;25(6):100812. doi: 10.1016/j.gim.2023.100812. Epub 2023 Apr 14. PMID: 37058144.
d. Rehder C, Bean LJH, Bick D, et al. Next-generation sequencing for constitutional variants in the clinical laboratory, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021 Aug;23(8):1399-1415. doi: 10.1038/s41436-021-01139-4. Epub 2021 Apr 29. PMID: 33927380.

Colorectal Cancer Screening

Stool-based DNA or RNA testing, i.e. Cologuard (81528)/Cologuard Plus (0464U) or Colosense (0421U), 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

Blood-based cell-free DNA testing for colorectal cancer is considered never medically necessary.

**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.*

Criteria listed above are based primarily on the following resources. Publications issued after this guideline's effective date will be evaluated on an individual basis until criteria are incorporated in the next iteration of this guideline.

a. Barnell EK, Kang Y, Barnell AR, et al. Multitarget Stool RNA Test for Noninvasive Detection of Colorectal Neoplasias in a

Multicenter, Prospective, and Retrospective Cohort. Clin Transl Gastroenterol. 2021 May 24;12(5):e00360. doi: 10.14309/ctg.0000000000000360. PMID: 34029233; PMCID: PMC8148418.
b. Issaka RB, Chan AT, Gupta S. AGA Clinical Practice Update on Risk Stratification for Colorectal Cancer Screening and Post-Polypectomy Surveillance: Expert Review. Gastroenterology. 2023 Nov;165(5):1280-1291. doi: 10.1053/j.gastro.2023.06.033. Epub 2023 Sep 21. PMID: 37737817; PMCID: PMC10591903.
c. National Comprehensive Cancer Network (NCCN) Guidelines. Colorectal Cancer Screening. v.1.2025. Accessed at: https://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf
d. US Preventive Services Task Force, Davidson KW, Barry MJ, et al. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2021 May 18;325(19):1965-1977. doi: 10.1001/jama.2021.6238. Erratum in: JAMA. 2021 Aug 24;326(8):773. PMID: 34003218.
e. U.S. Food & Drug Administration. Premarket Approval. Multi-Target Stool DNA (mtsDNA) Test, Cologuard Plus™. Updated on 05/19/2025. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P230043.
f. Wolf AMD, Fontham ETH, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin. 2018 Jul;68(4):250-281. doi: 10.3322/caac.21457. Epub 2018 May 30. PMID: 29846947.

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.

Criteria listed above are based primarily on the following resources. Publications issued after this guideline's effective date will be evaluated on an individual basis until criteria are incorporated in the next iteration of this guideline.

a. Kashani-Sabet M, Leachman SA, Stein JA, et al. Early Detection and Prognostic Assessment of Cutaneous Melanoma: Consensus on Optimal Practice and the Role of Gene Expression Profile Testing. JAMA Dermatol. 2023 May 1;159(5):545-553. doi: 10.1001/jamadermatol.2023.0127. PMID: 36920356.
b. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Melanoma: Cutaneous. v.3.2025. Accessed at https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf
c. Swetter SM, Tsao H, Bichakjian CK, et al. Guidelines of care for the management of primary cutaneous melanoma. J Am Acad Dermatol. 2019 Jan;80(1):208-250. doi: 10.1016/j.jaad.2018.08.055. Epub 2018 Nov 1. PMID: 30392755.

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.

Criteria listed above are based primarily on the following resources. Publications issued after this guideline's effective date will be evaluated on an individual basis until criteria are incorporated in the next iteration of this guideline.

a. Ali SZ, Baloch ZW, Cochand-Priollet B, et al. The 2023 Bethesda System for Reporting Thyroid Cytopathology. Thyroid. 2023 Sep;33(9):1039-1044. doi: 10.1089/thy.2023.0141. Epub 2023 Jul 8. PMID: 37427847.
b. Livhits MJ, Zhu CY, Kuo EJ, et al. Effectiveness of Molecular Testing Techniques for Diagnosis of Indeterminate Thyroid Nodules: A Randomized Clinical Trial. JAMA Oncol. 2021 Jan 1;7(1):70-77. doi: 10.1001/jamaoncol.2020.5935. PMID: 33300952; PMCID: PMC7729582.
c. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Thyroid Carcinoma. V1.2025. Accessed at: https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf.
d. Patel KN, Yip L, Lubitz CC, et al. The American Association of Endocrine Surgeons Guidelines for the Definitive Surgical Management of Thyroid Disease in Adults. Ann Surg. 2020 Mar;271(3):e21-e93. doi: 10.1097/SLA.0000000000003580. PMID: 32079830.
e. Steward DL, Carty SE, Sippel RS, et al. Performance of a Multigene Genomic Classifier in Thyroid Nodules With Indeterminate Cytology: A Prospective Blinded Multicenter Study. JAMA Oncol. 2019 Feb 1;5(2):204-212. doi: 10.1001/jamaoncol.2018.4616. Erratum in: JAMA Oncol. 2019 Feb 1;5(2):271. PMID: 30419129; PMCID: PMC6439562.

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.

Criteria listed above are based primarily on the following resources. Publications issued after this guideline's effective date will be evaluated on an individual basis until criteria are incorporated in the next iteration of this guideline.

a. American Cancer Society. Multi-cancer Early Detection (MCED) Tests. 2025 April. Available from: https://www.cancer.org/cancer/screening/multi-cancer-early-detection-tests.html
b. Merker JD, Oxnard GR, Compton C, et al. Circulating Tumor DNA Analysis in Patients With Cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. J Clin Oncol. 2018 Jun 1;36(16):1631-1641. doi: 10.1200/JCO.2017.76.8671. Epub 2018 Mar 5. PMID: 29504847.

Prostate Cancer Early Detection (Symptomatic Screening)

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

Criteria listed above are based primarily on the following resources. Publications issued after this guideline's effective date will be evaluated on an individual basis until criteria are incorporated in the next iteration of this guideline.

a. Mottet N, Cornford P, van den Bergh RCN, et al. EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer. European Association of Urology. [Internet]. 2023 March. Available from: https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-EANM-ESTRO-ESUR-ISUP-SIOG-Guidelines-on-Prostate-Cancer-2023.pdf.
b. Wei JT, Barocas D, Carlsson S, et al. Early detection of prostate cancer: AUA/SUO guideline part I: prostate cancer screening. J Urol. 2023;210(1):45-53.

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-cancer early detection (MCED) testing refers to non-invasive screening tests intended to detect cancer in individuals before they develop symptoms.

Multi-gene panels simultaneously analyze multiple genes associated with a particular condition or a group of related conditions.

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
0421U	Oncology (colorectal) screening, quantitative real-time target and signal amplification of 8 RNA markers (GAPDH, SMAD4, ACY1, AREG, CDH1, KRAS, TNFRSF10B, EGLN2) and fecal hemoglobin, algorithm reported as a positive or negative for colorectal cancer risk
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
0566U	Oncology (lung), qPCRbased analysis of 13 differentially methylated regions (CCDC181, HOXA7, LRRC8A, MARCHF11, MIR129-2, NCOR2, PANTR1, PRKCB, SLC9A3, TBR1_2, TRAP1, VWC2, ZNF781), pleural fluid, algorithm reported as a qualitative result

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.
v1.2026	COOC: 8/5/2025 PAB: 09/16/2025	January 9, 2026	Semi-annual review. General testing criteria were added. Colosense was added to the stool-based molecular testing criteria and a never medically necessary statement was added for blood based cfDNA based screening. CPT codes were updated. Key references were added as rationale under each criteria section replacing the formal reference section.