

05-82000-27

Original Effective Date: 08/15/03

Reviewed: 02/23/23

Revised: 07/01/24

Subject: Analysis of Human DNA as a Technique for Colorectal Cancer Screening

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions	Related Guidelines
Other	References	Updates			

DESCRIPTION:

Several genetic alterations have been associated with colorectal cancer (CRC). In the proposed multistep model of carcinogenesis, the tumor suppressor gene p53 and the proto-oncogene KRAS are most frequently altered. Variants in adenomatous polyposis coli genes and epigenetic markers (e.g., hypermethylation of specific genes) have also been detected. CRC is also associated with DNA replication errors in microsatellite sequences (termed microsatellite instability) in patients with Lynch Syndrome (formerly known as hereditary nonpolyposis CRC) and in subgroups of patients with sporadic colon carcinoma. Tumor-associated gene variants and epigenetic markers can be detected in exfoliated intestinal cells in stool specimens. Since cancer cells are shed into stool, tests have been developed to detect these genetic alterations in the DNA from shed CRC cells isolated from stool samples.

Assays that detect circulating methylated SEPT9 DNA have been proposed as a screening test for CRC. The Septin 9 protein is involved in cell division, migration, and apoptosis and acts as a tumor suppressor; when hypermethylated, expression of SEPT9 is reduced. There are various tests available however, performance characteristics vary across tests, presumably due to differences in methodology (eg, DNA preparation, PCR primers, probes).

POSITION STATEMENT:

The use of an FDA approved fecal DNA test (e.g. Cologuard™) **meets the definition of medical necessity** once every three years as a screening technique for members 45 - 75 years of age at average risk of colorectal cancer in whom colorectal cancer preventive screening is indicated.

The use of an FDA approved fecal DNA test is considered **experimental or investigational** for all other indications including post colorectal cancer diagnosis surveillance. The evidence is insufficient to determine the effects of the technology on health outcomes.

The use of non-FDA approved fecal DNA test and all other methods for the analysis of DNA in stool samples are considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes.

Septin 9 (SEPT9) DNA methylation assays (e.g. ColoVantage[®], Epi proColon[®]) are considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes

BILLING/CODING INFORMATION:

CPT Coding:

81327	SEPT9 (Septin9) (eg, colorectal cancer) promoter methylation analysis (Investigational)
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
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

HCPCS Coding:

G0327	Colorectal cancer screening; blood-based biomarker (Investigational)
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REIMBURSEMENT INFORMATION:

Refer to section entitled [POSITION STATEMENT](#).

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage products: The following National Coverage Determination (NCD) was reviewed on the last guideline reviewed date: Colorectal Cancer Screening Tests (210.3) located at cms.gov.

The following Local Coverage Determination (LCD) was reviewed on the last guideline reviewed date: Molecular Pathology Procedures (L34519).

DEFINITIONS:

Average Risk: Individuals with no prior diagnosis of CRC, adenomatous polyps, or inflammatory bowel disease; no personal diagnosis or family history of known genetic disorders that predispose them to a

high lifetime risk of colorectal cancer (such as Lynch syndrome or familial adenomatous polyposis).
(*USPSTF Colorectal Cancer: Screening, May 2021*)

RELATED GUIDELINES:

[01-99385-03, Preventive Services](#)

OTHER:

None Applicable.

REFERENCES:

1. Agency for Healthcare Research and Quality (AHRQ), Technology Assessment- Cost-Effectiveness of DNA Stool Testing to Screen for Colorectal Cancer, 12/07.
2. Ahlquist DA, Sargent DJ, Loprinzi CL, et al, Stool DNA and Occult Blood Testing for Screen Detection of Colorectal Neoplasia, *Annals of Internal Medicine*, 2008; 149: 441-450.
3. American Cancer Society[®]. American Cancer Society Guideline for Colorectal Cancer Screening-For people at average risk. Last Revised: November 17, 2020; accessed at cancer.org.
4. Berger, BM, et al. Screening for Colorectal Cancer Using a Multitarget Stool DNA Test: Modeling the Effect of the Intertest Interval on Clinical Effectiveness; *Clin Colorectal Cancer*. 2015 Dec 18. Pii: S1533-0028(15)00154-1. Doi: 10.1016/j.clcc.2015.12.003.
5. Berger B, et al, USPSTF Colorectal Cancer Screening Guidelines: An Extended Look at Multi-Year Interval Testing; *Am J Manag Care*. 2016;22(2):e77-e81.
6. Blue Cross Blue Shield Association Evidence Positioning System[®]. 2.04.29 Analysis of Human DNA in Stool Samples as a Technique for Colorectal Cancer Screening, 12/22.
7. Blue Cross Blue Shield Association Evidence Positioning System[®]. 2.04.150 Serologic Genetic and Molecular Screening for Colorectal Cancer, 08/22.
8. Blue Cross Blue Shield Association. Technology Evaluation Center. Special Report: Fecal DNA Analysis for Colorectal Cancer Screening. September 18, 2014.
9. Burke CA, Lieberman D, Feuerstein JD. AGA Clinical Practice Update on Approach to the Use of Noninvasive Colorectal Cancer Screening Options: Commentary. *Gastroenterology*. 2022 Mar;162(3):952-956.
10. Centers for Medicare & Medicaid Services (CMS), National Coverage Determination (NCD) for Colorectal Cancer Screening Tests (210.3), accessed at cms.gov.
11. Cole D, et al. Preferences for Colorectal Screening Tests Among a Previously Unscreened Population. *Proceedings of the 80th Annual American College of Gastroenterology*; 2015 October 16-21; Honolulu, HI. *Am J Gastroenterol*. 2015;110:S595-S628.
12. 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.
13. Diehl F, Schmidt K, Durkee K, et al, Analysis of Mutations in DNA Isolated From Plasma and Stool of Colorectal Cancer Patients, *Gastroenterology*, 03/08.

14. First Coast Service Options, Inc. (FCSO), Local Coverage Determination (LCD): Molecular Pathology Procedures (L34519), accessed at fcsso.com.
15. Gellad ZF, et al. Longitudinal adherence to fecal occult blood testing impacts colorectal cancer screening quality; *Am J Gastroenterol*. 2011 Jun;106(6):1125-34. Doi: 10.1038/ajg.2011.11. Epub 2011 Feb 8.
16. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med*. Apr 3 2014;370(14):1287-1297.
17. Inadomi JM, et al. Adherence to Colorectal Cancer Screening, A Randomized Clinical Trial of Competing Strategies; *Arch Intern Med*. 2012;172(7):575-582.
18. Itzkowitz S, Brand R, Jandorf L, et al, A Simplified, Noninvasive Stool DNA Test for Colorectal Cancer Detection, *AM J Gastroenterology*. 2008 Nov; 103(11):2862-70.
19. Ladabaum U, et al. Colorectal testing utilization and payments in a large cohort of commercially insured US adults; *Am J Gastroenterol*. 2014 Oct;109(10):1513-25. Doi: 10.1038/ajg.2014.64. Epub 2014 Jul 1.
20. Levin B, Lieberman D, McFarland B, et al, Screening and Surveillance for the Early Detection of Colorectal Cancer and Adenomatous Polyps, 2008: A Joint Guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology, *CA Cancer j Clin* 2008, accessed at amcancersoc.org 02/20/12.
21. Lin JS, Webber EM, Beil TL, et al. Fecal DNA Testing in Screening for Colorectal Cancer in Average-Risk Adults [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012 Feb. (Comparative Effectiveness Reviews, No. 52.); accessed at ncbi.nlm.gov.
22. National Comprehensive Cancer Network (NCCN), Clinical Practice Guidelines in Oncology- Colorectal Cancer Screening; accessed at nccn.org.
23. Parekh M, Fendrick AM, Ladabaum U, As Tests Evolve and Costs of Cancer Care Rise: Reappraising Stool-Based Screening for Colorectal Neoplasia, *Aliment Pharmacol Ther*. 2008 Apr; 27(8): 697-712.
24. Rex DK, Boland CR, Dominitz JA, et al. Colorectal cancer screening: recommendations for physicians and patients from the U.S. Multi-Society Task Force on Colorectal Cancer. *Am J Gastroenterol*. Jul 2017;112(7):1016-1030.
25. Song L, Jia J, et al, The performance of the SEPT9 gene methylation assay and a comparison with other CRC screening tests: A meta-analysis. *Sci Rep*. 2017 Jun 8;7(1):3032.
26. U.S. Food and Drug Administration (FDA); accessed at fda.gov.
27. U.S. Preventive Services Task Force (USPSTF). Final Recommendation Statement- Colorectal Cancer: Screening, May 2021; accessed at uspreventiveservicestaskforce.org.
28. 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*. May 30 2018.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Medical Policy and Coverage Committee on 02/23/23.

GUIDELINE UPDATE INFORMATION:

08/15/03	New Medical Coverage Guideline.
07/15/04	Scheduled review. No change in policy statement.
01/01/05	HCPCS update. Added S3890.
08/15/05	Scheduled review. No change in policy statement. Updated references and related Internet links.
08/15/06	Annual review; continue investigational.
07/15/07	Scheduled review; investigational status maintained, guideline reformatted, references updated.
09/15/08	Annual review: position statement maintained, description section and references updated.
07/15/09	Annual review: position statement maintained, description section and references updated.
05/15/10	Annual review: position statement maintained, description section and references updated.
04/15/12	Annual review; position statement maintained and references updated.
04/15/13	Annual review; position statement maintained and references updated.
04/15/14	Annual review; investigational position statement maintained, Medicare program exception and references updated.
01/01/15	Annual HCPCS/CPT update. Added code G0464.
04/15/15	Annual review; position statement maintained; program exception and references updated.
01/01/16	Annual HCPCS/CPT update; code 81528 added, codes G0464 and S3890 deleted.
05/15/16	Annual review; position statement section, description, program exception, and references updated.
08/12/16	Revisions to Position Statement.
12/15/16	Revision; position statement section and references updated.
01/01/17	Annual CPT/HCPCS update. Added 81327.
01/11/17	Revision; position statement section updated.
01/01/19	Annual CPT/HCPCS coding update. Revised code 81327.
02/15/19	Review: Position statements, title, description, program exception, and references updated.
03/15/21	Review; Position statement and references updated.
07/01/21	Quarterly CPT/HCPCS update. Code G0327 added.
01/01/22	Revision: Position statement and references updated.
10/01/22	Revision: References updated.
03/15/23	Review: Position statements maintained and references updated.
07/01/24	Quarterly CPT/HCPCS coding update. Code 0464U added.