05-82000-27

Original Effective Date: 08/15/03

Reviewed: 07/23/26

Revised: 08/15/26

Subject: Analysis of Human DNA/RNA and Serologic Genetic and Molecular Testing 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:

It is well established that early detection of colorectal cancer (CRC) reduces disease-related mortality. Forpatients at average risk for CRC, organizations such as the U.S. Preventive Services Task Force (USPSTF) have recommended several options for colon cancer screening. Currently accepted screening options for CRC include colonoscopy or sigmoidoscopy, fecal occult blood testing, and fecal immunochemical testing. However, many individuals do not undergo recommended screening with fecal tests or colonoscopy. Approximately 75% of colorectal cancer deaths occur in people who are not up to date with cancer screening. A simpler screening blood test for genetic alterations associated with non-familial CRC may have the potential to encourage screening and decrease mortality if associated with increased screening compliance. Genetic testing is alsobeing investigated to guide therapy.

Detection of DNA or RNA abnormalities associated with colorectal cancer (CRC) in stool samples has been proposed as a screening test for CRC. This technology is another potential alternative to currently available screening approaches, such as fecal occult blood testing, fecal immunochemical testing (FIT), and colonoscopy. The currently available stool tests combine FIT and DNA or RNA analysis and are referred to as FIT-DNA or FIT-RNA. The tests are also known as stool DNA (sDNA)-FIT, multitarget stool DNA (mt-sDNA) or multitarget stool RNA (mt-sRNA) test.

POSITION STATEMENT:

The use of an FDA approved fecal RNA test (e.g. Colosense®) or 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 RNA or 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.

Combination testing of DNA or RNA analysis of stool samples with other methods of colorectal cancer screening within a year is considered **experimental or investigational**.

The use of non-FDA approved fecal RNA test or DNA test and all other methods for the analysis of RNA or 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®, ColoHealth™) are considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes.

Gene expression profiling (e.g., ColonSentry®, BeScreened™ CRC) is considered **experimental or investigational** for colorectal cancer screening. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Epigenomic and genomic cell-free DNA (cfDNA) blood-based testing with Guardant Shield™ is considered **experimental or investigational** for colorectal cancer screening. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 [Cologuard]
0163U	Oncology (colorectal) screening, biochemical enzyme-linked immunosorbent assay (ELISA) of 3 plasma or serum proteins (teratocarcinoma derived growth factor-1 [TDGF-1, Cripto-1], carcinoembryonic antigen [CEA], extracellular matrix protein [ECM]), with demographic data (age, gender, CRC-screening compliance) using a proprietary algorithm and reported as likelihood of CRC or advanced adenomas [BeScreened CRC (**Investigational**)
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 [Colosense]
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, agorithm reported as a positive or negative result [Cologuard Plus]
0537U	Oncology (colorectal cancer), analysis of cell-free DNA for epigenomic patterns, next-generation sequencing, >2,500 differentially methylated regions (DMRs), plasma, algorithm reported as positive or negative [Shield] (**Investigational**)

HCPCS Coding:

G0327	Colorectal cancer screening; blood-based biomarker (**Investigational**)

REIMBURSEMENT INFORMATION:

Fecal RNA (e.g. Colosense) or DNA tests (e.g. Cologuard) will not be reimbursed when performed within 1 year after a completed colonoscopy.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage products: The following were reviewed on the last guideline reviewed date and are located at cms.gov: National Coverage Determination (NCD) Colorectal Cancer Screening Tests (210.3) and National Coverage Analysis Decision Memo: Screening for Colorectal Cancer-Non-Invasive Biomarker Tests, CAG-00440R.

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

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

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:

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Medical Policy and Coverage Committee on 07/23/26.

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.
02/15/25	Review: Position statements maintained; reimbursement and references updated.
08/15/26	Review: Position statements, description, title, reimbursement, coding, and references updated.