

<b>BSC_CON_2.09 Oncology: Cancer Screening</b>		
<b>Original Policy Date:</b>	February 1, 2023	<b>Effective Date:</b> March 1, 2023
<b>Section:</b>	2.0 Medicine	<b>Page:</b> Page 1 of 10

**Example Test Table**

Below is a list of higher volume tests and the associated laboratories for each coverage criteria section. This list is not all inclusive.

Policy Statement Sections	Example Tests (Labs)	Common CPT Codes
<b>COLORECTAL CANCER SCREENING TESTS</b>		
<a href="#">FIT-DNA Testing (Stool DNA Testing)</a>	Cologuard (Exact Sciences Corporation)	81528
<a href="#">Blood-based Biomarker Colorectal Cancer Screening Tests</a>	BeScreened (Beacon Biomedical)	0163U
	FirstSightCRC (CellMax Life)	0091U
	ColonSentry (StageZero Life Sciences)	81599
	Epi proColon (Epigenomics)	81327
	ColoVantage (Quest Diagnostics)	
<b>URINARY BIOMARKERS FOR CANCER SCREENING, DIAGNOSIS, AND SURVEILLANCE</b>		
<a href="#">Urinary Biomarker Tests for Bladder Cancer or Pre-cancerous Colon Polyps</a>	PolypDx(Metabolomic Technologies)	0002U
<b>LUNG CANCER SCREENING TESTS</b>		
<a href="#">Blood-based Biomarker Tests</a>	EarlyCDT-Lung (Oncimmune)	83520

**Policy Statement**

**COLORECTAL CANCER SCREENING TESTS**

**Fecal immunohistochemical testing(FIT)-DNA Testing (Stool DNA Testing)**

- I. The use of [FIT-DNA](#) Testing (stool DNA testing) (81528) to screen for colorectal cancer may be considered **medically necessary** when:
  - A. The member is 45 years of age or older, **AND**
  - B. The member is an individual who is at average risk for colorectal cancer, because the member does not have any of the following:
    1. A personal history of colorectal cancer or adenoma or sessile serrated polyp
    2. A family history of colorectal cancer
    3. A personal history of inflammatory bowel disease (ulcerative colitis or Crohn’s disease)
    4. A confirmed or suspected hereditary colorectal cancer syndrome, such as familial adenomatous polyposis (FAP) or Lynch syndrome (hereditary non-polyposis colon cancer or HNPCC)
    5. A personal history of receiving radiation to the abdomen (belly) or pelvic area to treat a prior cancer
  
- II. The use of FIT-DNA Testing (stool DNA testing) (81528) to screen for colorectal cancer is considered **investigational** for all other indications. Other types of screening may be appropriate when FIT-DNA testing is not appropriate.

**Note:** Fecal immunochemical testing ([FIT](#)) alone is not in the scope of this policy (see [definitions](#))

### Blood-based Biomarker Colorectal Cancer Screening Tests

- III. The use of blood-based biomarkers to screen for colorectal cancer (0091U, 0163U, 81327, 81599) is considered **investigational**.

## URINARY BIOMARKERS FOR CANCER SCREENING, DIAGNOSIS, AND SURVEILLANCE

### Urinary Biomarker Tests for Bladder Cancer or Pre-cancerous Colon Polyps

- IV. The use of urinary tumor markers is considered **investigational** in the screening, diagnosis of, and monitoring for bladder cancer, or screening for precancerous colonic polyps (0002U).

## LUNG CANCER SCREENING TESTS

### Blood-based Biomarkers

- V. The use of blood-based biomarker tests (83520) for lung cancer screening are considered **investigational**.

**NOTE:** Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

## Policy Guidelines

### Notes and Definitions:

**Fecal immunohistochemical testing (FIT)** is a screening test for colon cancer that detects human blood in the lower intestines. (FIT testing alone does not involve any genetic test and is outside of the scope of this policy).

**FIT-DNA test** combines fecal immunochemical (FIT), which uses antibodies to detect blood in the stool, with a test that detects abnormal DNA from cancer or polyp cells in the stool.

**Low-dose computed tomography (LDCT)** has been proposed as a method of screening asymptomatic, high risk individuals for lung cancer; it refers to a non contrast study with a multi-detector CT scanner during a single maximal inspiratory breath-hold with a scanning time of under 25 seconds. It has been suggested that LDCT may be an improved early lung cancer detection tool based on the advantages it appears to have over CXR and sputum cytology to detect lung cancer at an earlier stage.

**MicroRNAs (miRNAs)** are tissue specific, small, non-coding RNAs regulating gene expression which may identify candidates for early detection of lung cancer.

### CLINICAL CONSIDERATIONS

Screening tests are not diagnostic tests. The results from a screening test put an individual into a lower risk or higher risk status. For an individual that is put into the higher risk status, following up with an appropriate diagnostic test would be necessary to make a definitive diagnosis of cancer.

For lung cancer in particular, approaches in which a biomarker based initial screen is followed by low-dose computed tomography (LDCT) or in which a biomarker test is combined with LDCT show promise for use in early detection. However, at this time more high quality evidence is needed to support and guide the implementation of these tests.

## Description

This policy relates to genetic and biomarker tests that aim to screen for specific cancers in individuals who are at risk to develop them. These screening tests can be designed for asymptomatic individuals that are at an average risk level for cancer, or for individuals that are known to be at a higher risk to

develop a specific cancer. Genetic and biomarker cancer screening tests aim to identify the presence of cancer before symptoms appear and when treatment is often most effective. These tests are not currently diagnostic for cancer, but typically determine if an individual has an increased chance that cancer is present.

Screening tests for colorectal cancer may be performed by analyzing specific DNA present in fecal matter or peripheral blood. Cancer screening tests may also be performed on urine samples to screen for bladder cancer and colon polyps. These methods offer a noninvasive alternative to currently available screening approaches such as colonoscopy.

Screening tests for lung cancer are potentially useful adjuncts to the low-dose CT (LDCT), a recommended lung cancer screening tool in high-risk populations. Biomarkers such as autoantibodies, metabolites, proteins, and microRNA may be sampled from many different bodily sources, including whole blood, serum, plasma, bronchial brushings, and sputum. Circulating blood-based and serum based biomarkers are a convenient compartment to sample as they are relatively easy and inexpensive to collect.

## Related Policies

This policy document provides coverage criteria for cancer screening tests. Please refer to:

- **Oncology: Molecular Analysis of Solid Tumors and Hematologic Malignancies** for criteria related to DNA testing of a solid tumor or a blood cancer. *(To be published)*
- **Genetic Testing: Hereditary Cancer Susceptibility Syndromes** for criteria related to genetic testing to determine if an individual has an inherited cancer susceptibility syndrome. *(To be published)*
- **Oncology: Algorithmic Testing** for criteria related to gene expression profiling and tumor multianalyte assays with algorithmic analyses. *(To be published)*
- **Oncology: Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy)** for criteria related to circulating tumor DNA (ctDNA) or circulating tumor cell testing performed on peripheral blood for cancer diagnosis, management and surveillance. *(To be published)*
- **Genetic Testing: General Approach to Genetic Testing** for coverage criteria related to cancer screening that is not specifically discussed in this or another non-general policy. *(To be published)*

## Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

## Rationale

### Background

#### Colon Cancer Screening Tests

##### *National Comprehensive Cancer Network (NCCN)*

Current NCCN guidelines on colorectal cancer screening (1.2022) support the use of FIT-DNA in average-risk individuals aged 45-75 who might have a life expectancy  $\geq 10$  years, and notes that the decision to screen individuals aged 76-85 should be individualized.

Current NCCN guidelines (1.2022) do not include a recommendation for colorectal cancer screening via blood-based or urine-based screening.

##### *US Preventative Services Task Force (USPSTF)*

The USPSTF published an updated recommendation statement (2021) on screening for colorectal cancer that included the following:

"The USPSTF recommends screening for colorectal cancer in all adults aged 50 to 75 years. (A recommendation) The USPSTF recommends screening for colorectal cancer in adults aged 45 to 49 years. (B recommendation) The USPSTF recommends that clinicians selectively offer screening for colorectal cancer in adults aged 76 to 85 years. Evidence indicates that the net benefit of screening all persons in this age group is small. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the patient's overall health, prior screening history, and preferences. (C recommendation)"

The USPSTF published a recommendation statement (2021) on screening for lung cancer that included the following:

"The USPSTF recommends annual screening for lung cancer with low dose computed tomography (LCDT) in adults aged 50 to 80 years who have a 20 pack year smoking history and currently smoke or have quit within the past 15 years.

"Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery."

"A rating of A and B from the USPSTF applies to the Affordable Care Act (ACA) preventative services. This recommendation is Grade B."

##### *US Food and Drug Administration (FDA)*

###### **Cologuard (Exact Sciences):**

On August 12, 2014, Cologuard (Exact Sciences) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process as an automated fecal DNA testing product (P130017). Cologuard is intended for the qualitative detection of colorectal neoplasia associated with DNA markers and occult hemoglobin in human stool. A positive result may indicate the presence of CRC or advanced adenoma and should be followed by diagnostic colonoscopy.

On September 20, 2019, the FDA approved the expansion of the Cologuard label to include adults ages  $\geq 45$  years. Cologuard was previously indicated for those  $\geq 50$  years. Cologuard is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high-risk individuals.

###### **Epi ProColon (Epigenomics):**

On April 12, 2014, Epi ProColon (Epigenomics) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process as a qualitative in vitro diagnostic test for the detection of methylated Septin 9 DNA in EDTA plasma derived from patient whole blood

specimens (P130001). The FDA approval notes that, “the Epi proColon test is indicated to screen adults of either sex, 50 years or older, defined as average risk for CRC, who have been offered and have a history of not completing CRC screening. Tests that are available and recommended in the USPSTF 2008 CRC screening guidelines should be offered and declined prior to offering the Epi proColon test. Patients with a positive Epi proColon test result should be referred for diagnostic colonoscopy. The Epi proColon test results should be used in combination with physician's assessment and individual risk factors in guiding patient management.”

### Lung Cancer Screening Tests

#### ***National Comprehensive Cancer Network (NCCN)***

Current NCCN guidelines on lung cancer screening (1.2022) does not recommend lung cancer screening via blood-based or micro-RNA based screening. Current NCCN guidelines support lung cancer screening using LDCT for individuals with high risk factors.

### Concert Genetics Technical Assessment 2021

#### **Blood-based Biomarker Tests**

This review focused on peer-reviewed, published evidence of the clinical utility of BeScreened, FirstSight CRC, ColonSentry, Epi ProColon, and Colovantage through October 2021. PubMed and ECRI Guidelines Trust searches were performed. Search terms included BeScreened, FirstSight CRC, ColonSentry, Epi ProColon, Colovantage, colon cancer screen, circulating tumor cells, Cripto, ANXA3, CLEC4D, LMNB1, PRRG4, TNFAIP6, VNN1, SEPT9. References were also identified from the performing laboratory's website. A total of 60 abstracts from these sources were reviewed, and 17 full text publications were evaluated. At the present time, BeScreened, FirstSight CRC, ColonSentry, Epi ProColon, and Colovantage have not been adequately shown in peer-reviewed publications to effectively result in improved health outcomes compared to the current standard of care.

## References

1. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colorectal Cancer Screening. Version 1.2022.  
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2. US Preventive Services Task Force, Davidson KW, Barry MJ, et al. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2021;325(19):1965-1977. doi:10.1001/jama.2021.6238
3. Summary of Safety and Effectiveness Data (SSED): Cologuard™. U.S. Food & Drug Administration website. Available at:  
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4. Summary of Safety and Effectiveness Data (SSED): Epi proColon®. U.S. Food & Drug Administration website. Available at:  
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8. Hanash SM, Ostrin EJ, Fahrman JF. Blood based biomarkers beyond genomics for lung cancer screening. *Transl Lung Cancer Res*. 2018;7(3):327-335. doi:10.21037/tlcr.2018.05.13
9. Concert Genetics. Technology Assessment Summary of Blood Based Biomarkers for Colorectal Cancer. 2021.

## Documentation for Clinical Review

### Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Clinical findings (i.e., pertinent symptoms and duration) as applicable
  - Family history, if applicable
  - Reason for procedure/test
  - Pertinent past procedural and surgical history
  - Past and present diagnostic or screening testing and results if applicable
- Previous pertinent laboratory results

### Post Service (in addition to the above, please include the following):

- Results/reports of tests performed
- Procedure report(s)

## Coding

*This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.*

*The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.*

Type	Code	Description
CPT®	0002U	Oncology (colorectal), quantitative assessment of three urine metabolites (ascorbic acid, succinic acid and carnitine) by liquid chromatography with tandem mass spectrometry (LC-MS/MS) using multiple reaction monitoring acquisition, algorithm reported as likelihood of adenomatous polyps
	0012M	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm reported as a risk score for having urothelial carcinoma
	0013M	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm reported as a risk score for having recurrent urothelial carcinoma
	0091U	Oncology (colorectal) screening, cell enumeration of circulating tumor cells, utilizing whole blood, algorithm, for the presence of adenoma or cancer, reported as a positive or negative result
	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

Type	Code	Description
	0363U	Oncology (urothelial), mRNA, gene-expression profiling by real-time quantitative PCR of 5 genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm incorporates age, sex, smoking history, and macrohematuria frequency, reported as a risk score for having urothelial carcinoma <i>(Code effective 1/1/2023)</i>
	81327	SEPT9 (Septin9) (e.g., colorectal cancer) promoter methylation analysis
	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
	81599	Unlisted multianalyte assay with algorithmic analysis
	83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
	86294	Immunoassay for tumor antigen, qualitative or semiquantitative (e.g., bladder tumor antigen)
	86316	Immunoassay for tumor antigen, other antigen, quantitative (e.g., CA 50, 72-4, 549), each
	86386	Nuclear Matrix Protein 22 (NMP22), qualitative
	88120	Cytopathology, in situ hybridization (e.g., FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; manual
	88121	Cytopathology, in situ hybridization (e.g., FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; using computer-assisted technology
HCPCS	None	

## Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
02/01/2023	New policy.
03/01/2023	Coding update.

## Definitions of Decision Determinations

**Medically Necessary:** Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.



**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

### Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at [www.blueshieldca.com/provider](http://www.blueshieldca.com/provider).

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: [MedPolicy@blueshieldca.com](mailto:MedPolicy@blueshieldca.com)

*Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.*



**Appendix A**

POLICY STATEMENT	
BEFORE <u>Red font: Verbiage removed</u>	AFTER <u>Blue font: Verbiage Changes/Additions</u>
<p><b>Urinary Biomarkers for Cancer Screening, Diagnosis, and Surveillance 2.04.07</b></p> <p>Policy Statement:</p>	<p><b>Oncology: Cancer Screening BSC_CON_2.09</b></p> <p>Policy Statement:</p> <p><b>COLORECTAL CANCER SCREENING TESTS</b></p> <p><b>Fecal immunohistochemical testing(FIT)-DNA Testing (Stool DNA Testing)</b></p> <ol style="list-style-type: none"> <li>I. The use of <u>FIT-DNA Testing</u> (stool DNA testing) (81528) to screen for colorectal cancer may be considered <b>medically necessary</b> when:               <ol style="list-style-type: none"> <li>A. The member is 45 years of age or older, <b>AND</b></li> <li>B. The member is an individual who is at average risk for colorectal cancer, because the member <u>does not</u> have any of the following:                   <ol style="list-style-type: none"> <li>1. A personal history of colorectal cancer or adenoma or sessile serrated polyp</li> <li>2. A family history of colorectal cancer</li> <li>3. A personal history of inflammatory bowel disease (ulcerative colitis or Crohn’s disease)</li> <li>4. A confirmed or suspected hereditary colorectal cancer syndrome, such as familial adenomatous polyposis (FAP) or Lynch syndrome (hereditary non-polyposis colon cancer or HNPCC)</li> <li>5. A personal history of receiving radiation to the abdomen (belly) or pelvic area to treat a prior cancer</li> </ol> </li> </ol> </li> <li>II. The use of FIT-DNA Testing (stool DNA testing) (81528) to screen for colorectal cancer is considered <b>investigational</b> for all other indications. Other types of screening may be appropriate when FIT-DNA testing is not appropriate.</li> </ol> <p><b>Note:</b> Fecal immunochemical testing (<u>FIT</u>) alone is not in the scope of this policy (see <u>definitions</u>)</p>

POLICY STATEMENT

<p style="text-align: center;"><b>BEFORE</b></p> <p style="text-align: center;"><b>Red font: Verbiage removed</b></p>	<p style="text-align: center;"><b>AFTER</b></p> <p style="text-align: center;"><b>Blue font: Verbiage Changes/Additions</b></p>
<p>The use of urinary tumor markers is considered <b>investigational</b> in the screening, diagnosis of, and monitoring for bladder cancer, or screening for precancerous colonic polyps.</p>	<p><b>Blood-based Biomarker Colorectal Cancer Screening Tests</b></p> <p>III. The use of blood-based biomarkers to screen for colorectal cancer (0091U, 0163U, 81327, 81599) is considered <b>investigational</b>.</p> <p><b>URINARY BIOMARKERS FOR CANCER SCREENING, DIAGNOSIS, AND SURVEILLANCE</b></p> <p><b>Urinary Biomarker Tests for Bladder Cancer or Pre-cancerous Polyps</b></p> <p>IV. The use of urinary tumor markers is considered <b>investigational</b> in the screening, diagnosis of, and monitoring for bladder cancer, or screening for precancerous colonic polyps (0002U).</p> <p><b>LUNG CANCER SCREENING TESTS</b></p> <p><b>Blood-based Biomarkers</b></p> <p>V. The use of blood-based biomarker tests (83520) for lung cancer screening are considered <b>investigational</b>.</p>