



BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

Analysis of Human DNA in Stool Samples as a Technique for Colorectal Cancer Screening

Policy # 00003

Original Effective Date: 08/25/2003

Current Effective Date: 11/16/2016

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member's contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider analysis of stool samples using the Cologuard^{®†} multi-targeted stool deoxyribonucleic acid (DNA) test as a screening technique for colorectal cancer at intervals of one test every three years to be **eligible for coverage**.

Patient Selection Criteria

Cologuard multi-targeted stool deoxyribonucleic acid (DNA) test as a screening technique for colorectal cancer will be eligible for coverage in patients meeting all of the following criteria:

- Age 50 to 85 years, AND
- Asymptomatic (no signs or symptoms of colorectal disease including but not limited to lower gastrointestinal pain, blood in stool, positive guaiac fecal occult blood test or fecal immunochemical test), AND
- At Average risk of developing colorectal cancer (no personal history of adenomatous polyps, colorectal cancer (CRC), or inflammatory bowel disease, including Crohn's disease and ulcerative colitis; no family history of colorectal cancers, familial adenomatous polyposis, or hereditary nonpolyposis colorectal cancer)

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers deoxyribonucleic acid (DNA) analysis of stool samples as a screening technique for colorectal cancer when patient selection criteria are not met or using any stool deoxyribonucleic acid (DNA) test other than Cologuard to be **investigational**.*

Background/Overview

Detection of genetic abnormalities associated with 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), or colonoscopy.

Several cellular genetic alterations have been associated with CRC. In the proposed multistep model of carcinogenesis, the tumor suppressor gene *p53* and the proto-oncogene *KRAS* are most frequently altered.

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Mutations in *APC* (adenomatous polyposis coli) genes and epigenetic markers (e.g., hypermethylation of specific genes) have also been detected. Colorectal cancer is also associated with DNA replication errors in microsatellite sequences (termed microsatellite instability or MSI) in patients with Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer (HNPCC)) and in a subgroup of patients with sporadic colon carcinoma. Tumor-associated gene mutations and epigenetic markers can be detected in exfoliated intestinal cells in stool specimens. Since cancer cells are shed into stool, tests have been developed that detect these genetic alterations in the DNA from shed CRC cells isolated from stool samples.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

On August 12, 2014, Cologuard™[‡] (Exact Sciences) was approved by the 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 DNA markers and for the presence of occult hemoglobin in human stool. A positive result may indicate the presence of CRC or advanced adenoma and should be followed by diagnostic colonoscopy. Cologuard is indicated to screen adults of either sex, 50 years or older, who are at average risk for CRC. Cologuard is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high-risk individuals.

Over the past several years, different stool DNA tests have been evaluated in studies and some have been marketed. One of previously marketed tests, PreGen-Plus™[‡], tests for 21 different mutations in the *p53*, *APC*, and *K-ras* genes; the BAT-26 MSI marker; and incorporates the DNA Integrity Assay (DIA®)[‡]. PreGen-Plus has not been cleared by FDA. On January 13, 2006, FDA sent correspondence to LabCorp indicating that PreGen-Plus may be subject to FDA regulation as a medical device. As a consequence, and as a result of studies showing better performance of other tests, this test is no longer offered. Another previously marketed test is called ColoSure™[‡], developed by OncoMethylome Sciences, which detects aberrant methylation of the vimentin (*hV*) gene. This test was offered as a laboratory-developed test, not subject to FDA regulation.

Centers for Medicare and Medicaid Services (CMS)

On October 9, 2014, a CMS Decision Memo was issued indicating Medicare Part B will cover the Cologuard test once every 3 years for beneficiaries who meet all of the following criteria:

- Age 50 to 85 years,
- Asymptomatic (no signs or symptoms of colorectal disease including but not limited to lower gastrointestinal pain, blood in stool, positive guaiac fecal occult blood test or fecal immunochemical test), and
- At average risk of developing CRC (no personal history of adenomatous polyps, colorectal cancer, or inflammatory bowel disease, including Crohn's Disease and ulcerative colitis; no family history of CRCs or adenomatous polyps, familial adenomatous polyposis, or hereditary nonpolyposis colorectal cancer).

All other screening stool DNA tests not otherwise specified above remain nationally noncovered.



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As noted in the CMS Decision Memo, the optimal screening interval for Cologuard is unknown. In the interim, CMS indicates it will provide coverage for Cologuard every 3 years as previously specified, and will reevaluate the screening interval after the Cologuard after FDA approval study is completed.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Analysis of Human DNA in Stool Samples as a Technique for Colorectal Cancer Screening", 2.04.29, 11:2015.
2. Centers for Medicare and Medicaid Services (CMS). Proposed Decision Memo for Screening for Colorectal Cancer - Stool DNA Testing (CAG-00440N). 2014; <http://www.cms.gov/medicare-coverage-database/details/nca-proposed-decision-memo.aspx?NCAId=277>. Accessed 11/17/14.
3. U.S. Preventive Services Task Force. Colorectal cancer: Screening U.S. Preventive Services Task Force Published Recommendation. Release Date: June 2016.

Policy History

Original Effective Date:	08/25/2003
Current Effective Date:	11/16/2016
08/19/2003	Medical Policy Committee review
08/25/2003	Managed Care Advisory Council approval
08/03/2005	Medical Director review
08/16/2005	Medical Policy Committee review. No change to coverage eligibility.
08/24/2005	Managed Care Advisory Council approval
07/07/2006	Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
05/02/2007	Medical Director review
05/23/2007	Medical Policy Committee approval. Coverage eligibility unchanged.
05/07/2009	Medical Director review
05/20/2009	Medical Policy Committee approval. Coverage eligibility unchanged.
05/06/2010	Medical Director review
06/16/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/01/2011	Coding review
05/05/2011	Medical Director review
05/18/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/03/2012	Medical Policy Committee review
05/16/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/04/2013	Coding updated
05/02/2013	Medical Director review
05/22/2013	Medical Policy Implementation Committee approval. No change to coverage.
03/06/2014	Medical Policy Committee review
03/19/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2015	Coding updated

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04/02/2015 Medical Policy Committee review
04/20/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
01/01/2016 Coding update: CPT code added
04/07/2016 Medical Policy Committee review
04/20/2016 Medical Policy Implementation Committee approval. Added coverage statement for Cologuard testing every three years in patients meeting criteria.
11/03/2016 Medical Policy Committee review
11/16/2016 Medical Policy Implementation Committee approval. Adenomatous polyps removed from family history criteria. New reference added.
01/01/2017 Coding update: Removing ICD-9 Diagnosis codes
Next Scheduled Review Date: 11/2017

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2015 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81528
HCPCS	G0464
ICD-10 Diagnosis	All related diagnosis

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:



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1. Consultation with the Blue Cross and Blue Shield Association TEC or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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 that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

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