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: 05/10/2021

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 (CRC) 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 (CRC) 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 ([CRC] 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 [CRCs], familial adenomatous polyposis, or hereditary nonpolyposis colorectal cancer [HNPCC]).

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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 (CRC) when patient selection criteria are not met or using any stool deoxyribonucleic acid (DNA) test other than Cologuard to be **investigational.***

Background/Overview

Colorectal Cancer

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. Variants in adenomatous polyposis coli genes and epigenetic markers (eg, 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. Because cancer cells are shed into the stool, tests have been developed to 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 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 DNA markers and 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. On September 20, 2019, the FDA approved the expansion of the Cologuard label to include adults ages ≥45 years. Cologuard was previously indicated for those ≥50 years. Cologuard is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high-risk individuals. On August 26,

2020, the FDA approved the post-approval study (PAS) protocol titled: "A Real-World Study of Patients Under the Age of 50 Screened for Colorectal Cancer (CRC) Using Cologuard in the U.S. (Tidal)."

Over the past several years, different stool DNA tests have been evaluated in studies, and some have been marketed. One previously marketed test, PreGen-Plus™‡ (LabCorp), tests for 21 different variants in the *p53*, adenomatous polyposis coli, and *KRAS* genes; the BAT-26 microsatellite instability marker; and incorporates the DNA Integrity Assay (DIA®‡). PreGen-Plus has not been cleared by the FDA. In January 2006, the FDA informed LabCorp 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™‡ (OncoMethylome Sciences; now MDxHealth), which detects aberrant methylation of the vimentin (*hV*) gene. This test was offered as a laboratory-developed test and is not subject to FDA regulation.

Rationale/Source

Detection of DNA 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 DNA test combines FIT and DNA analysis and is referred to as FIT-DNA in this review.

For individuals who are asymptomatic and at average risk of CRC who receive FIT-DNA, the evidence includes a number of small studies comparing FIT-DNA (in early stages of development) with colonoscopy, two screening studies comparing the final version of the FIT-DNA (using colonoscopy as the reference standard), and modeling studies. The relevant outcomes are overall survival and disease-specific survival. The screening studies have reported that FIT-DNA has higher sensitivity and lower specificity than FIT. There are no studies directly assessing health outcomes such as overall survival or disease-specific survival. The test characteristics of FIT-DNA show the potential of the test to be an effective CRC screening test, but there is uncertainty about other aspects of it. The screening interval for the test has not been firmly established nor is there evidence on the adherence of the test at a recommended screening interval. Effective screening for CRC requires a screening program with established screening intervals and appropriate follow-up for positive tests.

Clinical utility of FIT-DNA is based on modeling studies. These studies have demonstrated that the diagnostic characteristics of FIT-DNA are consistent with decreases in CRC mortality that are in the range of other accepted modalities. FIT-DNA every three years is less effective than most other accepted screening strategies, while FIT-DNA every year is close to the efficacy of colonoscopy every ten years. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

Several recommendations of specialty organizations on stool DNA testing were based largely on the Imperiale et al (2004), which evaluated a different test and should be considered obsolete. This includes 2008 guidelines from the American Cancer Society, 2012 guidelines from the American College of Physicians, and 2009 guidelines from the American College of Gastroenterology.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network guidelines (v.2.2020) for colorectal cancer (CRC) screening includes the use of fecal immunochemical testing-DNA (FIT-DNA) to screen patients with an average risk for colon cancer. Following a negative test, the recommendation is to rescreen with any modality after three years. Use of FIT-DNA tests is not described for the screening of high-risk individuals. Follow-up colonoscopy is recommended within 6 to 10 months after a positive test.

Multi-Society Task Force on Colorectal Cancer

A U.S. Multi-Society task force representing the American College of Gastroenterology, the American Gastroenterological Association, and the American Society for Gastrointestinal Endoscopy (2017) provided recommendations for CRC screening. The recommended first-tier tests for individuals with average risk were colonoscopy every ten years, and for individuals who decline colonoscopy, annual FIT. Recommended second-tier tests in patients who declined the first-tier tests were computed tomography colonography every five years, FIT-DNA every three years, or flexible sigmoidoscopy every five to ten years. Capsule colonoscopy was listed as a third-tier test. The task force recommended, "[computed tomography] colonography every 5 years or FIT-fecal DNA every 3 years (strong recommendation, low-quality evidence, or flexible sigmoidoscopy every 5-10 years (strong recommendation, high-quality evidence) in patients who refuse colonoscopy and FIT."

American Cancer Society
The American Cancer Society (2018) updated its guidelines for CRC screening for average-risk adults. Regular screening with either a structural examination (ie, colonoscopy) or a high-sensitivity stool-based test is recommended to start in adults who are 45 years and older (qualified recommendation) or who are 50 years and older (strong recommendation). Recommendations for screening with stool-based tests include FIT repeated every year, high-sensitivity guaiac-based fecal occult blood test repeated every year, or multitarget stool DNA test repeated every three years.

U.S. Preventive Services Task Force Recommendations
In 2016, the U.S. Preventive Services Task Force Recommendations (USPSTF) published its most recent recommendations for CRC screening. CRC screening was recommended starting at age 50 years and continuing until age 75 years (A recommendation). The recommendation statement reviewed seven different screening strategies including FIT-DNA. Regarding comparisons of preferences between the seven different methods mentioned: "The USPSTF found no head-to-head studies demonstrating that any of the screening strategies it considered are more effective than others, although the tests have varying levels of evidence supporting their effectiveness, as well as different strengths and limitations…. The screening tests are not presented in any preferred or ranked order…." USPSTF noted that sensitivity of FIT-DNA is higher that with FIT, but specificity is lower "resulting in more false-positive results, more diagnostic colonoscopies, and more associated adverse events per screening test."

Medicare National Coverage
In 2014, a Centers for Medicare & Medicaid Services decision memo indicated 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 colorectal cancer (no personal history of adenomatous polyps, colorectal cancer, or inflammatory bowel disease, including Crohn's Disease and ulcerative colitis; no family history of colorectal cancers or adenomatous polyps, familial adenomatous polyposis, or hereditary nonpolyposis colorectal cancer).
- All other stool DNA tests not otherwise specified above remain nationally non-covered."

As noted in the Centers for Medicare & Medicaid Services decision memo, the optimal screening interval for Cologuard is unknown. In the interim, Centers for Medicare & Medicaid Services has indicated it will cover Cologuard every three years as previously specified and would reevaluate the screening interval after the Food and Drug Administration approval study is completed.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01647776	Screening and Risk Factors of Colon Neoplasia	1600	Jan 2021 (recruiting)
NCT04144738[a]	Clinical Validation of An Optimized Multi-Target Stool DNA (Mt-sDNA 2.0) Test, for Colorectal Cancer Screening "BLUE-C"	12500	Apr 2022 (recruiting)
NCT04124406[a]	Voyage: Real-World Impact of the Multi-target Stool DNA Test on CRC Screening and Mortality	150000	Dec 2029 (recruiting)
Unpublished			
NCT03728348[a]	An Evaluation of a Multi-target Stool DNA (Mt-sDNA) Test, Cologuard, for CRC Screening in Individuals Aged 45-49 and at Average Risk for Development of Colorectal Cancer: Act Now	983	Jun 2019 (completed)
NCT02419716[a]	A Longitudinal Study of Cologuard™ in an Average Risk Population Assessing a 3 Year Test Interval	2404	Mar 2020 (completed)

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

References

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Policy History

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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

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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
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
11/02/2017	Medical Policy Committee review
11/15/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/28/2018	Coding update
11/08/2018	Medical Policy Committee review
11/21/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Coding section removed.
11/07/2019	Medical Policy Committee review

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11/13/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/02/2020	Medical Policy Committee review
04/08/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/01/2021	Medical Policy Committee review
04/14/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 04/2022

*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. Food and Drug Administration (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:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (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.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.