Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines

Policy # 00237
Original Effective Date: 04/15/2009
Current Effective Date: 11/15/2017

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 Are 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 a one-time genotypic or phenotypic analysis of the enzyme thiopurine methyltransferase (TPMT) in patients beginning therapy with azathioprine (AZA), mercaptopurine (6-MP) or thioguanine (6-TG) or in patients on thiopurine therapy with abnormal complete blood count (CBC) results that do not respond to dose reduction to be eligible for coverage.

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 genotypic and/or phenotypic analysis of the enzyme thiopurine methyltransferase (TPMT) in all other situations to be investigational.*

Based on review of available data, the Company considers analysis of the metabolite markers of azathioprine (AZA) and mercaptopurine (6-MP), including 6-methyl-mercaptopurine ribonucleotides (6-MMPR) and 6-thioguanine nucleotides (6-TGN) to be investigational.*

Background/Overview
Several cellular 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 K-ras are most frequently altered. Mutations in APC (adenomatous polyposis coli) genes and epigenetic markers (e.g., hypermethylation of specific genes) have also been detected. CRC is also associated with deoxyribonucleic acid (DNA) replication errors in microsatellite sequences (termed microsatellite instability [MSI]) in patients with Lynch syndrome (formerly known as hereditary nonpolyposis CRC) and in subgroups of patients with sporadic colon carcinoma. Tumor-associated gene mutations and epigenetic markers can be detected in exfoliated intestinal cells in stool specimens. Because 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.
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**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. 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. 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 previously marketed test, PreGen-Plus™ (LabCorp.), 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. In January 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™ (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.

Centers for Medicare and Medicaid Services (CMS)

In October 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, CRC, 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 CRC)."

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

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

**Rationale/Source**

The important outcome of interest in cancer screening is a reduction in the mortality and morbidity due to cancer. This is ideally determined with randomized clinical trials. However, for colon cancer screening, many of the recommended tests have not been evaluated with clinical trials. The efficacy of these tests is
supported by numerous studies evaluating the diagnostic characteristics of the test for detecting cancer and cancer precursors along with a well-developed body of knowledge on the natural history of the progression of cancer precursors to cancer. Modeling studies have evaluated the robustness and quantity of health benefit of various screening tests when clinical trial evidence is lacking.

When lacking direct evidence that a screening test reduces cancer mortality, the critical parameters in the evaluation are the diagnostic performance characteristics (i.e., sensitivity, specificity, positive and negative predictive value) compared with a criterion standard, the proposed frequency of screening, and the follow-up management of test results. The diagnostic performance characteristics of the currently accepted screening options (i.e., fecal occult blood testing, fecal immunochemical testing [FIT], flexible sigmoidoscopy, double-contrast barium enema) have been established using colonoscopy as the criterion standard. Modelling studies and clinical trial evidence on some of the screening modalities have allowed some confidence on the effectiveness of several cancer screening modalities.

For patients at average risk for CRC, organizations such as the U.S Preventive Services Task Force have recommended several options for colon cancer screening. Advocates of DNA testing of stool samples have hypothesized that the relative simplicity of collecting a stool sample might increase the overall compliance with screening recommendations compared to imaging or direct visualization screening strategies, and tests that detect cancer-associated DNA in stool may be superior to current stool tests for the detection of cancer and cancer precursors.

Because there are no studies of stool DNA testing for screening individuals at high risk of CRC, the evidence discussed pertains only to screening of individuals at average risk of CRC. The evidence discussed herein is restricted to studies evaluating Cologuard, the only test approved by the FDA, which combines FIT and DNA analysis; we will called it FIT-DNA throughout.

**FIT-DNA TEST**

**Diagnostic Accuracy**

Preliminary studies of the FIT-DNA (Cologuard), which was eventually evaluated in the large-scale screening study by Imperiale et al, were conducted by Ahlquist et al and Lidgard et al. This multitarget FIT-DNA consists of quantitative measurements of molecular assays for aberrantly methylated $\text{BMP3}$ and $\text{NDRG4}$ promoter regions, mutant $\text{KRAS}$, $\beta$-actin, and hemoglobin in a logistic-regression algorithm. Because it includes a FIT in its algorithm, it is actually a combined stool DNA and FIT. In a study of 252 patients with CRC, 133 patients with adenomas of 1 cm or larger, and 293 subjects with normal colonoscopy, the test detected 85% of colon cancer cases and 54% of subjects with adenomas, with 90% specificity. Another smaller study of this same test showed a sensitivity of 87% for detecting CRC and 82% sensitivity for detecting adenomas. In the study by Lidgard et al, of 1003 patients, there were 207 cases with CRC or advanced adenomas (>1 cm) and 796 control patients with no polyps or nonadvanced adenomas (<1 cm). In the case group, 93 subjects had CRC, 84 had advanced adenoma 1 cm or larger, and 30 had sessile serrated adenoma 1 cm or larger. In the control group, 155 subjects had nonadvanced adenomas and 641 had no colonic lesions. Using a logistic regression algorithm that incorporates 11...
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markers into a single regression score and a fixed specificity of 90%, FIT-DNA identified 84 (98% sensitivity) of 86 CRCs and 41 (56% sensitivity) of 73 advanced adenoma cases. These preliminary studies all evaluated stool DNA using preassembled samples of study subjects with and without cancer or colonic lesions. For diagnostic characteristics of tests evaluated in these types of study samples may be biased.

A large-scale evaluation of this test in a screening population was published in 2014 by Imperiale et al, who compared the FIT-DNA in 12,000 asymptomatic persons at average risk for CRC. The results of this study supported the U.S. FDA approval of this fecal DNA test (Cologuard) in August 2014. All enrolled subjects were scheduled to undergo screening colonoscopy. Stool specimens were collected and tested no more than 90 days before the screening colonoscopy. Screening colonoscopy findings were considered the reference standard for determining the diagnostic characteristics of FIT-DNA for detecting CRC and cancer precursors. In 9989 evaluable subjects, FIT-DNA sensitivity for cancer was 92.3% (95% CI, 83.0 to 97.5) and for FIT it was 73.8% (95% CI, 61.5 to 84.0). For advanced precancerous lesion, fecal DNA test sensitivity was 42.4% (95% CI, 38.9 to 46.0) and for FIT it was 23.8% (95% CI, 20.8 to 27.0). In analyses of specific types of lesions, sensitivity of the FIT-DNA did not vary by cancer stage or cancer location. Among patients with advanced precancerous lesions, the sensitivity of fecal DNA testing was higher for distal lesions than for proximal lesions. FIT-DNA sensitivity increased as lesion size increased. The specificity of the FIT-DNA was lower than that of FIT. For identification of patients with insignificant lesions and negative colonoscopy, specificity of the FIT-DNA was 86.6% (95% CI, 85.9 to 87.2) and 94.9% (95% CI, 94.4 to 95.3) for FIT. For identification of patients only with negative colonoscopy, specificity of the FIT-DNA was 89.8% (95% CI, 88.9 to 90.7) and 96.4% (95% CI, 95.8 to 96.9) for FIT.

A second evaluation of FIT-DNA was published in 2016 by Redwood et al. Asymptomatic Alaska natives undergoing screening or surveillance colonoscopy were enrolled in the study. Colonoscopy findings were considered the reference standard for determining the diagnostic characteristics of the FIT-DNA and FIT for detecting CRC and cancer precursors. In 661 evaluable subjects, FIT-DNA sensitivity for cancer was 100% and for FIT it was 85%. For screening-relevant neoplasms (defined as adenoma or sessile serrated adenoma/polyp ≥1 cm, any adenoma with ≥25% villous component, or cancer), FIT-DNA sensitivity was 49% and 28% for FIT. Specificities for FIT-DNA were lower than FIT. When all patients with no screening-relevant neoplasms were considered normal, specificities were 91% for FIT-DNA and 94% for FIT. When only patients without any polyps were considered normal, specificities were 93% for FIT-DNA and 96% for FIT.

Section Summary: Diagnostic Accuracy
The 2 studies of FIT-DNA are consistent with each other in that both have demonstrated the higher sensitivity of FIT-DNA than for FIT for both CRC detection and cancer precursor detection, but lower specificity. The study by Imperiale is more than 10 times the size of that by Redwood and thus represents the best estimate of the diagnostic performance of FIT-DNA in a single screening.

Clinical Utility
There are no studies evaluating direct health outcomes of a longitudinal screening program using Cologuard. In 2014, a TEC Special Report evaluated FIT-DNA for CRC screening. The report found the
Imperiale study to be of good quality but noted while FIT-DNA had higher sensitivity than FIT for various types of colorectal lesions, these results represented the diagnostic characteristics of the FIT-DNA in a 1-time cross-sectional study. How these study results would translate to reduced colorectal mortality in a longitudinal screening program has not been directly assessed. The optimal screening interval is unknown. However, decision modelling may help inform the effectiveness of CRC screening by indirect means.

In 2016, Knudsen et al compared different CRC screening strategies using microsimulation modeling techniques to inform the U.S. Preventive Services Task Force CRC screening recommendations (see Table 1). Diagnostic characteristics of FIT-DNA from the study by Imperiale et al were incorporated into the model and screening outcomes from various screening strategies were estimated and compared. FIT-DNA was evaluated in these models using both a yearly screening strategy and an every 3-year strategy. The modeling results suggested that stool DNA screening produces outcomes within the range of the other screening strategies. FIT-DNA every 3 years is at the lower range of effectiveness, only higher than flexible sigmoidoscopy, and testing every year is at the higher range of effectiveness, only lower than colonoscopy every 10 years. In terms of complications or lifetime burden as expressed as colonoscopies, FIT-DNA appears to be in the range of other CRC screening strategies, with every year screening having higher complication and colonoscopy rates than every 3 year screening. Both measures of harm were estimated to be lower than the screening strategy of colonoscopy every 10 years. The analysis proposed a set of screening modalities that were considered model-recommendable, based on having at least 90% of the life-year gain of colonoscopy, and having met certain efficiency criteria. FIT-DNA was not selected as a model-recommended strategy because it was not considered as efficient as other stool-based strategies.

Another modeling study, sponsored by the manufacturer of Cologuard, showed similar findings. Compared to colonoscopy every 10 years, yearly FIT-DNA was estimated to produce similar reductions in CRC incidence and mortality. Every 3-year and every 5-year testing produced less reduction in CRC incidence and mortality. Colonoscopy every 10 years was estimated to decrease CRC incidence by 65%, whereas FIT-DNA every 3 years reduced CRC incidence by 57% and FIT-DNA every 5 years reduced CRC incidence by 52%.

<table>
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<tr>
<th>Screening Method and Screening Interval</th>
<th>Life-Years Gained per 1000 Screened</th>
<th>CRC Deaths Averted per 1000 Screened</th>
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SUMMARY OF EVIDENCE

For individuals who are asymptomatic and at average risk of CRC who receive FIT and DNA analysis (FIT-DNA), the evidence includes a number of small studies comparing FIT-DNA (in early stages of development) with colonoscopy, 2 screening studies comparing the final version of the FIT-DNA (using colonoscopy as the reference standard), and 2 modelling studies. Relevant outcomes are overall survival, disease-specific survival, and test accuracy. The 2 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 the test. 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. Modelling studies comparing different screening strategies have demonstrated that the diagnostic characteristics of FIT-DNA as shown in the existing studies are consistent with decreases in CRC mortality that are in the range of other accepted modalities. FIT-DNA every year is estimated to be close to but not as effective as colonoscopy every 10 years. FIT-DNA every 3 years is estimated to be less effective than most of the other accepted screening strategies. Estimates of harms and burdens are in the range of other screening strategies, but the test was considered less efficient than other methods. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

References

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05/07/2009 Medical Director review
05/20/2009 Medical Policy Committee approval. New policy.
06/03/2010 Medical Policy Committee approval
06/16/2010 Medical Policy Implementation Committee approval. Policy title changed by taking out azathioprine (6-MP) and replacing it with “Thiopurines”. Policy statement changed to “a one-time genotypic or phenotypic analysis of the thiopurine methyltransferase (TPMT) gene in patients beginning therapy with azathioprine (AZA), mercaptopurine (6-MP) or thioguanine (6-TG) or in patients on thiopurine therapy with abnormal complete blood count (CBC) results that do not respond to dose reduction to be eligible for coverage.”
06/02/2011 Medical Policy Committee review
06/14/2012 Medical Policy Committee review
06/20/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/11/2013 Codes updated.
06/06/2013 Medical Policy Committee review
06/05/2014 Medical Policy Committee review
06/18/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
09/03/2015 Medical Policy Committee review
09/23/2015 Medical Policy Implementation Committee approval. Statement added that genotypic and/or phenotypic analysis of the enzyme TPMT is considered investigational in all other situations.
11/03/2016 Medical Policy Committee review
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
11/02/2017 Medical Policy Committee review
04/01/2018 Coding update
Next Scheduled Review Date: 11/2018

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

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*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;

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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.

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