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

### Summary
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), or colonoscopy. The currently available stool DNA test combines FIT and DNA analysis and will be referred to as FIT-DNA in this review.

### FDA REGULATORY STATUS
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. 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.

### POLICY STATEMENT
DNA analysis of stool samples can be considered medically necessary as a screening technique for colorectal cancer in patients at average risk of colorectal cancer.
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DNA analysis of stool samples is considered investigational for all other indications.

**BENEFIT APPLICATION**

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

**RATIONALE**

**Summary of Evidence**

For individuals who are asymptomatic and at average risk of colorectal cancer (CRC) who receive fecal immunochemical testing (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.

**SUPPLEMENTAL INFORMATION**

**Practice Guidelines and Position Statements**

**National Comprehensive Cancer Network**

The 2015 National Comprehensive Cancer Network guidelines (v.1.2016) for colorectal (CRC) reviewed the study of Cologuard by Imperiale et al, and do not currently recommend FIT-DNA as a primary screening modality. However, FIT-DNA is listed in the set of stool-based screening strategies options, with the caveat that the screening interval is uncertain, but cites Berger et al as recommending every 3 years.

**U.S. Preventive Services Task Force Recommendations**

The U.S. Preventive Services Task Force (USPSTF) published its most recent recommendations for CRC screening in June 2016. CRC screening is recommended starting at age 50 years and continuing until age 75 years (A recommendation). The recommendation statement reviews 7 different screening strategies including FIT-DNA. Regarding comparisons or preferences between the 7 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.”
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Medicare National Coverage

In October 2014, a Centers for Medicare & Medicaid Services (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 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 Food and Drug Administration approval study is completed.

REFERENCES

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POLICY HISTORY

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<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tbody>
<tr>
<td>March 2015</td>
<td>New Policy</td>
<td>Policy updated with literature review through September 1, 2016: references 5, 7-8, and 13-14. References deleted. Policy statement changed from investigational to medically necessary for average risk patients. DNA analysis of stool samples is considered investigational for all other indications. Policy only applies to FIT-DNA.</td>
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<tr>
<td>December 2016</td>
<td>Revised Policy</td>
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Signature on File

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