Stool DNA–based Screening Test (Cologuard) for Detecting DNA and Hemoglobin Biomarkers Associated with Colorectal Cancer and Precancer

Executive Summary

Cologuard® (Exact Sciences, Madison, WI, USA) is a multitarget stool DNA–based colorectal cancer (CRC) screening test for patients age 50 years or older who are at average risk for CRC. To undergo testing with Cologuard, a patient receives a prescription from a primary care provider, collects a stool sample at home, and ships the sample to the manufacturer for analysis. On the basis of modeling studies, Cologuard’s manufacturer recommends that patients with negative test results undergo additional Cologuard testing at three-year intervals, although no clinical studies are available to support this interval. Patients with positive results are recommended to undergo follow-up diagnostic colonoscopy. Cologuard’s intended advantages include higher sensitivity for detecting CRC and advanced precancerous lesions than fecal immunochemical stool testing and a lower risk of adverse events than invasive CRC screening tests. Potential disadvantages include possible false test results. False-positive results could result in unnecessary colonoscopy and associated risks. False-negative results could delay additional evaluation and treatment for CRC.

Parameter Rating and Definition*

<table>
<thead>
<tr>
<th>Parameter Rating and Definition*</th>
<th>Rationale</th>
</tr>
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<tbody>
<tr>
<td><strong>Reimbursement Status:</strong> 4 Wide Coverage</td>
<td>The U.S. Centers for Medicare &amp; Medicaid Services issued a national coverage determination in October 2014 to cover Cologuard screening. The American Medical Association assigned the Current Procedural Terminology code 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 positive or negative result,” to describe Cologuard. Our searches of 10 representative, third-party payers found 4 major payers with a coverage policy for Cologuard and 6 payers with policies that deny coverage. Moderate per-patient cost (&gt; $2,000 to $5,000), or a moderate number of patients are expected to undergo this test at a cost &lt;$2,000 per test. Cologuard’s list price is $649. In the United States, approximately 69 million adults are candidates for CRC screening. If a significant proportion of patients who use fecal occult blood testing switch to Cologuard and a proportion of patients who have never undergone screening decide to use Cologuard testing, the test’s aggregate cost to payers will be moderate. Medicare’s 2016 Clinical Laboratory Fee Schedule includes reimbursement for the test at $508.87.</td>
</tr>
<tr>
<td><strong>Cost Impact on Payers:</strong> 3 Moderate</td>
<td>Exact Sciences stated it completed Cologuard tests for 104,000 patients in 2015 and 94,000 patients in the first half of 2016, totaling 252,000 tests. More than 41,000 physicians have prescribed Cologuard since its introduction (August 2014), including physicians from 57 large U.S. medical groups. Exact Sciences projects completing more than 240,000 Cologuard tests in 2016.</td>
</tr>
</tbody>
</table>

*Please see Appendix C for parameter definitions
**Evidence Summary of Selected Outcomes***

<table>
<thead>
<tr>
<th>Key Outcomes Assessed</th>
<th>GRADE-based Strength-of-evidence Rating</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity for detecting colorectal cancer</td>
<td>MODERATE</td>
<td>Cologuard is more sensitive than fecal immunochemical testing.</td>
</tr>
<tr>
<td>Sensitivity for detecting advanced precancerous lesions</td>
<td>MODERATE</td>
<td>Cologuard is more sensitive than fecal immunochemical testing.</td>
</tr>
<tr>
<td>Specificity for detecting the absence of colorectal cancer and advanced precancerous lesions</td>
<td>MODERATE</td>
<td>Fecal immunochemical testing is more specific than Cologuard.</td>
</tr>
</tbody>
</table>

*Note: We grade strength of evidence based on the concepts and methods proposed by the GRADE working group using ratings of very low, low, moderate, and high. We list outcomes we deem of greatest importance to patients first. See Appendix A for details. See the Findings section for additional outcomes for which we did not assess strength of evidence.

The best-available evidence on this technology came from two diagnostic cohort studies, which served as the basis for the GRADE ratings we assigned. No studies compared Cologuard’s diagnostic accuracy with that of any other colorectal cancer (CRC) screening method or reported on Cologuard’s effect on CRC-related mortality or CRC incidence. Other CRC screening methods include colonoscopy, flexible sigmoidoscopy, computed tomography colonography, double contrast barium enema, and high-sensitivity guaiac fecal occult blood test.
# Table of Contents

Executive Summary ........................................................................................................... 1
Evidence Summary of Selected Outcomes* ........................................................................ 2
Overview .......................................................................................................................... 1
  Background/Disease ........................................................................................................ 1
  Genetic Test Description: Cologuard .............................................................................. 3
Cost .................................................................................................................................. 4
Cost-effectiveness and Considerations .............................................................................. 4
Reimbursement .................................................................................................................. 5
  Coverage ......................................................................................................................... 5
  Patient Protection and Affordable Care Act ................................................................. 7
  State Mandates ............................................................................................................. 7
  Coding ............................................................................................................................ 8
  Payment .......................................................................................................................... 8
Regulatory Status ............................................................................................................. 8
FDA Manufacturer and User Facility Device Experience Database Reports ................... 9
Clinical Guidelines and Standards ................................................................................... 9
Evidence Reports Published by Other Health Technology Assessment Organizations ....... 11
Evidence Review .............................................................................................................. 11
  Patient Population and Outcomes of Interest ............................................................. 12
  Methods ......................................................................................................................... 12
Findings ............................................................................................................................ 14
  Clinical Validity ........................................................................................................... 14
  Clinical Utility ............................................................................................................. 15
Ongoing Clinical Trials ..................................................................................................... 15
Discussion ......................................................................................................................... 15
Genetic Test Significance: Evidence-base Conclusions and ECRI Institute Opinion .......... 17
References ....................................................................................................................... 18
Classifications .................................................................................................................. 26
Search Strategy ................................................................................................................ 27
Appendix A. Strength-of-evidence Assessment Methods ................................................... 28
  Risk-of-bias Assessment for Test Performance Studies ............................................... 28
  Risk-of-bias Assessment for Comparative Studies ....................................................... 29
Stool DNA-based Screening Test (Cologuard) for Detecting DNA and Hemoglobin Biomarkers Associated with Colorectal Cancer and Precancer

Appendix B. Results of Risk-of-bias and Strength-of-evidence Assessment........................................................................................................30
Appendix C. Impact Ratings Definitions..........................................................................................................................................................31
Policy Statement............................................................................................................................................................................................................32

Tables
Table 1. Colorectal Cancer Screening Methods .................................................................................................................................................1
Table 2. Third-party Payer Policies .................................................................................................................................................................6
Table 3. Cologuard Results by Patient Colonoscopy Result as Reported in FDA SSED ..........................................................................................14
Table 4. Ongoing Clinical Trials.................................................................................................................................................................15
Table 5. Cologuard Test Results in Hypothetical Screening Population .........................................................................................................16
Stool DNA–based Screening Test (Cologuard) for Detecting DNA and Hemoglobin Biomarkers Associated with Colorectal Cancer and Precancer

Overview

For the purpose of ECRIgene Evidence Reports, we use the 2008 definition of genetic tests developed by the U.S. Department of Health and Human Services Secretary’s Advisory Committee on Genetics, Health, and Society. This definition states that a genetic or genomic test involves an analysis of human chromosomes, DNA, RNA, genes, and/or gene products (e.g., enzymes, other types of proteins), which are predominantly used to detect heritable or somatic mutations, genotypes, or phenotypes related to disease and health.

Background/Disease

Colorectal Cancer

Colorectal cancer (CRC)—abnormal or uncontrolled cell growth in the colon or rectum—typically develops from benign growths, commonly called polyps, that grow on the inside walls of the colon or rectum. The two main types of polyps are adenomatous polyps (adenomas), which have the potential to develop into cancer, and hyperplastic or inflammatory polyps. Patients generally do not develop polyps until they are older than 50 years of age, and polyps typically transform from benign to cancerous over the course of 3 to 10 years. According to the American Cancer Society (ACS), CRC was the third most commonly diagnosed cancer and the third leading cause of cancer death in 2014. ACS estimates in 2016 physicians will diagnose 95,270 new cases of colon cancer and 39,220 new cases of rectal cancer and that 49,190 patients will die of CRC.

Because precancerous polyps and early-stage CRCs can typically be treated successfully by surgical resection, screening not only detects, but can also prevent CRC.

The goal of CRC screening is to identify patients who may have CRC or precancerous polyps. The U.S. Preventive Services Task Force (USPSTF) recommends that patients between the ages of 50 and 75 years who are at average risk (with no predisposing factors) of CRC undergo screening. Guidelines from the American College of Physicians and the American College of Gastroenterology recommend clinicians encourage patients to undergo colonoscopy as the preferred screening method. See Table 1 for information about CRC screening methods other than Cologuard. All the screening methods listed, except for colonoscopy, require follow-up diagnostic colonoscopy for patients with positive results. For patients who cannot or refuse to undergo colonoscopy, guidelines recommend shared decision making and discussion of alternative screening methods. For patients who have been offered and have declined the testing methods listed in Table 1, the U.S. Food and Drug Administration (FDA) has approved a blood-based qualitative CRC screening test, Epi proColon® (Epigenomics AG, Berlin, Germany), which 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.” Physicians recommend that patients with positive Epi proColon results undergo follow-up colonoscopy.

Table 1. Colorectal Cancer Screening Methods

<table>
<thead>
<tr>
<th>Screening Method</th>
<th>Recommended Screening Interval</th>
<th>Sensitivitya</th>
<th>Morbidity and Mortality Outcomes Reported in Clinical Studies</th>
<th>Intended Advantages and Potential Disadvantagesb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscopy</td>
<td>10 years</td>
<td>CRC: &gt;95%13</td>
<td>Inferred 60% to 70% reduction in CRC mortality14b</td>
<td>Advantages: Examines entire colon, allows immediate polypectomy, high accuracy, long screening interval Disadvantages: Risk of serious complications (e.g., perforation, bleeding), requires thorough bowel preparation, requires some sedation, performance may be operator dependent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AA: 88% to 98%13</td>
<td></td>
<td></td>
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<tr>
<td>Flexible sigmoidoscopy</td>
<td>5 years</td>
<td>CRC: 58% to 95%13 (in the distal colon)</td>
<td>Reduces CRC mortality by 28% and CRC incidence by 18%16,17</td>
<td>Advantages: Allows immediate polypectomy, requires enema-based bowel preparation Disadvantages: Risk of serious complications (e.g., perforation, bleeding), does not examine proximal colon, performance may be operator dependent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AA: 70% to 86%13 (in the distal colon)</td>
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</tbody>
</table>
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Policy Statement
ECRIgene Evidence Reports present profiles and literature reviews of new and emerging genetic tests. Each ECRIgene Evidence Report is designed to provide a snapshot of the current status, efficacy, and use of that technology. The information contained in ECRIgene Evidence Reports is derived primarily from the currently available, published, peer-reviewed scientific literature, trade publications, and World Wide Web sites. Publications referenced are generally limited to the English language. Often, there is a relative paucity of published clinical data on new and emerging technologies; therefore, information from health technology resources on the Internet and elsewhere may be included. The conclusions and recommendations in any ECRIgene Evidence Report must be interpreted cautiously and judiciously. The data on which they are based are often insufficient to permit unequivocal resolution of the scientific and clinical issues most relevant to patient care. ECRI Institute implies no warranty and assumes no liability for the information, conclusions, and recommendations contained in ECRIgene Evidence Reports.

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