Stool DNA Colorectal Cancer Screening Test Dossier

Evidence for Coverage
LABORATORY INFORMATION

The Cologuard® test is a proprietary test provided by Exact Sciences Laboratories, LLC. Cologuard is exclusively processed at Exact Sciences Laboratories, LLC and is not available through any other laboratory. Cologuard is a sole-sourced test; there are no other labs that offer a comparable stool DNA test for colorectal cancer screening.

Exact Sciences Laboratories, LLC has a Clinical Laboratory Improvement Amendments (CLIA) Certification of Accreditation and is College of American Pathologists (CAP) accredited. It holds Clinical Laboratory Licenses/Permits in New York, Florida, Illinois, Maryland, Rhode Island, California and Pennsylvania.

Exact Sciences Laboratories, LLC is located in the state of Wisconsin, and services patients in all U.S. states, territories and the District of Columbia.

Full prescribing information is available at www.cologuardtest.com/hcp.

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ABBREVIATIONS

AA .................................... Advanced Adenoma
ACG .................................. American College of Gastroenterology
ACP .................................. American College of Physicians
ACS .................................. American Cancer Society
AJCC .................................. American Joint Committee on Cancer
AMA .................................. American Medical Association
CAP .................................. College of American Pathologists
CDC .................................. Centers for Disease Control and Prevention
CISNET ................................. Cancer Intervention and Surveillance Modeling Network
CLIA .................................. Clinical Laboratory Improvement Amendments
CMS .................................. Centers for Medicare and Medicaid Services
CRC .................................. Colorectal Cancer
CTAF .................................. California Technology Assessment Forum
CTC .................................. CT Colonoscopy, Virtual Colonoscopy
DeeP-C ................................. Multi-Target Colorectal Cancer Screening Test for the Detection of Colorectal Advanced Adenomatous Polyps and Cancer Study
DNA .................................. Deoxyribonucleic Acid
FIT .................................. Fecal Immunochemical Test (immunologically Based Fecal Occult Blood Test)
FIT-DNA .............................. this term is used to describe Cologuard (mt-sDNA) is USPSTF recommendations
FDA .................................. Food and Drug Administration
FS ....................................... Flexible Sigmoidoscopy
gFOBT ................................. Guaiac-based Fecal Occult Blood Test
HCP .................................. Health Care Provider
HGD .................................. High Grade Dysplasia
iFOBT ................................. Immunochemical Fecal Occult Blood Test
LCA .................................. Laboratory Corporation of America
MA ..................................... Medicare Advantage
mt-sDNA Test ........................ Multi-Target Stool DNA Test (i.e., Cologuard™)
MSTFCRC ............................. Multi-Society Task Force on Colorectal Cancer
NAA .................................. Non-Advanced Adenoma
NCD .................................. National Coverage Determination
NCHS .................................. National Center for Health Statistics
NCI .................................. National Cancer Institute
PMA .................................. Premarket Approval
QuARTS ................................. Quantitative Allele-specific Real-time Target and Signal
QALY .................................. Quality-Adjusted Life-Year
RCT .................................. Randomized, Controlled Trial
sDNA .................................. Stool DNA Test (i.e., the category of stool DNA Tests or the earlier tests which are not Multi-Target, such as PreGenPlus and ColoSure)
SRN .................................. Screening-Relevant Colorectal Neoplasia
SSA .................................. Sessile Serrated Adenoma
TEC Criteria .......................... BCBSA Technology Evaluation Center Criteria
USPSTF ................................. United States Preventive Services Task Force
I. EXECUTIVE SUMMARY

Cologuard, the first and only multitarget stool DNA (mt-sDNA) test, is a noninvasive colorectal cancer (CRC) screening test developed by Exact Sciences Corporation, approved by the U.S. Food and Drug Administration (FDA), covered by Centers for Medicare and Medicaid Services (CMS), and available by prescription for use by average risk adults ages 50 years and older. Cologuard was the first medical product to successfully navigate the joint FDA-CMS parallel review process\(^\text{1}\); receiving premarket approval (PMA) from the FDA on August 11, 2014\(^\text{2}\) and a CMS National Coverage Decision (NCD) on October 9, 2014.\(^\text{3}\) Results from the DeeP-C study\(^\text{4}\), a pivotal, prospective 90-site, 10,000 patient cross-sectional clinical study were published in the New England Journal of Medicine in March 2014. The DeeP-C study compared mt-sDNA (Cologuard) and fecal immunochemical test (FIT), using colonoscopy as the reference standard on all cases. Cologuard demonstrated sensitivity at 92% of that seen with colonoscopy in detecting CRC, and demonstrated sensitivity significantly greater than in detecting CRC and advanced adenomas (AAs) (Table 1).\(^\text{4}\)

The momentum toward increasing coverage of Cologuard has continued to grow as the findings of the DeeP-C Study were corroborated by the Redwood study recently published in the The Mayo Clinic Proceedings.\(^\text{5}\) In this study, 661 patients were screened using a similar study design to the DeeP-C Study; the sensitivity of Cologuard was found to be 100% of that seen with colonoscopy in terms of detecting CRC and again superior to that seen with FIT for detecting CRC and AAs (Table 2). Based on these two robust clinical studies, and the positive decisions of FDA and CMS, numerous commercial health plans have extended coverage to Cologuard as the data describing its performance on these two robust clinical studies, and the positive decisions of FDA and CMS, detecting CRC and AAs significantly greater than in detecting CRC and advanced adenomas (AAs) (Table 1).\(^\text{4}\)

CRC is a serious public health concern. It is the third most commonly diagnosed cancer in the U.S. and the second most common cause of cancer death for men and women combined.\(^\text{6}\) Fortunately, CRC and death from CRC are largely preventable with universal, systematic screening; survival rates improve dramatically in patients with CRC detected at an early stage. For instance, when CRC is detected early (Stage I), the five-year survival rate is more than 90% with surgery alone (without chemotherapy).\(^\text{7}\) Universal CRC screening programs have been a primary component in the battle to reduce CRC morbidity and are recommended in guidelines addressing this topic. Unfortunately, compliance with these guideline recommendations has remained disappointingly low.\(^\text{6,8}\)

The Centers for Disease Control and Prevention (CDC) calculates that in 2013, the most recent data available, only 57.8% of Americans aged 50–75 were in compliance with the recommended CRC screening guidelines.\(^\text{6,8}\) This low number is directly responsible for much of the morbidity and mortality seen from CRC at the present time in the U.S. and leads the USPSTF to conclude in its recent draft recommendations that “the best screening test is the one that gets done.”\(^\text{9}\)

Colorectal cancer screening guidelines issued by the American Cancer Society (ACS) recommends the use of Cologuard every three years.\(^\text{10}\) The United States Preventive Services Task Force (USPSTF) recommends the use of sDNA testing as an “alternative test” for the detection of CRC.\(^\text{9}\) The American College of Physicians (ACP),\(^\text{11}\) American College of Gastroenterology (ACG),\(^\text{12}\) the California Technology Assessment Forum (CTAF)\(^\text{13}\), and the United States Multi-Society Task Force (MSTFCRC)\(^\text{14}\), and all include either sDNA, mt-sDNA, or Cologuard in their CRC screening guidelines. ECRI Institute concluded that Cologuard is more sensitive than FIT for for detecting CRC and advanced precancerous lesions and assigned a grade of ”Moderate” for the strength of evidence supporting this conclusion.
Cologuard demonstrates a compelling combination of high sensitivity in detecting CRC, good specificity, and low barriers to patient adoption with the potential to improve CRC mortality rates.

Cologuard uses a stool specimen collected from a patient at home to measure 10 DNA biomarkers combined with a highly sensitive FIT test for stool hemoglobin to generate a “Positive” or “Negative” result. A “Positive” result may indicate the presence of CRC or AA and should be followed by diagnostic colonoscopy. Stool specimens are shipped directly from the patient to Exact Sciences Laboratories for test performance. As such, a Cologuard test does not require a separate HCP office visit. Cologuard testing includes an embedded 24/7 patient navigation system utilizing a U.S. based call center that supports 70 languages to ensure adherence with the CRC screening order.

The important facts to consider when evaluating Cologuard for coverage are:

1. Cologuard provides CRC screening with high sensitivity, the highest of any noninvasive test and with good specificity as demonstrated in the DeeP-C study published in the New England Journal of Medicine (Table 1).

Table 1 Findings from the DeeP-C cross-sectional study, comparing mt-sDNA with FIT using colonoscopy as the reference standard on all cases (N=9989 subjects)

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Colonoscopy findings n detected</th>
<th>Cologuard % detected</th>
<th>FIT % detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal cancer (Stages I-IV)</td>
<td>65</td>
<td>92.3%</td>
<td>73.8%</td>
</tr>
<tr>
<td>Early stage Colorectal Cancer (Stage I and II)</td>
<td>50</td>
<td>94.0%</td>
<td>70.0%</td>
</tr>
<tr>
<td>Advanced adenoma (AA)</td>
<td>757</td>
<td>42.4%</td>
<td>23.8%</td>
</tr>
<tr>
<td>High grade dysplasia</td>
<td>39</td>
<td>69.2%</td>
<td>46.2%</td>
</tr>
<tr>
<td>Sessile Serrated Adenoma/Polyp ≥1.0 cm</td>
<td>99</td>
<td>42.4%</td>
<td>5.1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specificity</th>
<th>Cologuard % detected</th>
<th>FIT % detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity (only CRC and AA excluded)</td>
<td>9167</td>
<td>86.6%</td>
</tr>
<tr>
<td>Specificity, no adenomas, no biopsy done</td>
<td>4457</td>
<td>89.8%</td>
</tr>
<tr>
<td>Age-adjusted (50-74 yrs)</td>
<td>4032</td>
<td>92.3%</td>
</tr>
</tbody>
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Cologuard's high sensitivity and good specificity are further supported by the Redwood study published in the Mayo Clinic Proceedings (Table 2).

Table 2: Summary of findings from the Redwood study

<table>
<thead>
<tr>
<th>n=661</th>
<th>Cologuard</th>
<th>FIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection of CRC</td>
<td>100%</td>
<td>80%</td>
</tr>
<tr>
<td>Detection of Screening Relevant Neoplasms</td>
<td>49%</td>
<td>28%</td>
</tr>
<tr>
<td>Clean Colon Specificity (no neoplasms) (n=334)</td>
<td>93%</td>
<td>96%</td>
</tr>
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</table>
2. Cologuard lies at the center of a noninvasive CRC screening system designed to level the barriers to patient acceptance and promote high compliance rates. Since its launch, Cologuard, in conjunction with the Exact Sciences Laboratories compliance program, has achieved a greater than 70% test completion rate within 60 days of kit shipment to the patient. This compares to 40-45% real-world compliance with FIT, fecal occult blood testing (FOBT), and guaiac fecal occult blood testing (gFOBT).

- The USPSTF draft recommendation states that "clinicians should consider engaging patients in informed decision-making about the screening strategy that would most likely result in completion, with high adherence over time, taking into consideration both the patient’s preferences and local availability." Data demonstrates that there is a significant improvement in patient compliance when patients are offered a choice between a noninvasive screening option (67%) versus invasive colonoscopy (38%) (p < 0.001).

- A recent patient preference study found that previously noncompliant patients prefer mt-sDNA by more than 50% over colonoscopy or FIT when educated about CRC screening options.

- A recent longitudinal study of a more than 150,000-subjects demonstrates that one third of eligible adults over 50 failed to be adherent with the annual colorectal cancer screening recommendations of the USPSTF over a ten-year period. The study, published in American Journal of Managed Care, further shows that only three in a thousand people (0.3 percent) were adherent with annual colorectal cancer screening using either FIT or FOBT during a continuous 10-year observation period.

3. Three papers published in 2016 demonstrate the clinical utility of Cologuard through the use of modeling data.

- Data published in the peer-reviewed journal *Clinical Colorectal Cancer* uses the Archimedes cost-effectiveness model to support a three-year testing interval for Cologuard. The model demonstrates that Cologuard used every three years compares favorably to colonoscopy every 10 years. The analysis shows a colorectal cancer incidence reduction of 57 percent and mortality reduction of 67 percent, compared to 65 and 73 percent, respectively, for colonoscopy every 10 years.

- A peer-reviewed paper in the February, 2016 issue of the American Journal of Managed Care uses CISNET modeling data from the USPSTF Technical Report to demonstrate that Cologuard used at a three-year interval is within 98% of the USPSTF’s efficiency frontier and is the only noninvasive test to generate greater than 90% of the LYG by screening colonoscopy at 10-year interval.

- A peer-reviewed paper, in-press in the online publication World Journal of Gastrointestinal Oncology uses the USPSTF Technical Report CISNET modeling data to demonstrate the efficacy of Cologuard at three-year intervals and demonstrates across 1000 screened individuals, age 50-74, that it yields a median of 226 life-years gained, averts 20 CRC deaths, reduces CRC mortality by 76%, and produces the most benefit (LYG) per complication. The data further demonstrates that the number of colonoscopies per LYG generated by Cologuard at three-year intervals is equivalent to annual FIT and lower than hsFOBT.

4. An UpToDate article about Colorectal Cancer screening dated December 07, 2015 and authored by Doubeni, et al. includes the use of Cologuard every three years as a CRC screening option for average-risk patients and goes on to say "Cologuard stool DNA testing is an option for patients who would prefer not to undergo colonoscopy, but who are able and willing to undergo colonoscopy if the stool test is positive."
5. Over half (56.5%) of all Americans ages 50 and older currently have coverage for Cologuard as a CRC screening test.\textsuperscript{25}
   - Since October 9, 2014, CMS has extended coverage to Cologuard through NCD 210.3 (Colon Cancer Screening Tests). Cologuard is covered as frequently as every three years for use in asymptomatic patients age 50-85 who are at average risk for CRC.\textsuperscript{3}
   - When taken together, the many commercial health plans where Cologuard is covered constitute over 55 million lives. To date, all of these extend coverage with a frequency of every three years.\textsuperscript{25}
   - As a result, over 110 million Americans currently have access to Cologuard as a covered benefit, nearly one third of the U.S. population.\textsuperscript{25}
   - CRC screening is mandated in approximately seventeen states and the District of Columbia, which together represent 37.7% of the U.S. population, requiring coverage of Cologuard.\textsuperscript{26}

6. Published national commercial health plan claims data shows that colonoscopy cost to health plans averages $2,146.\textsuperscript{27,28} Cologuard list price is approximately thirty percent of this amount.

7. On January 1, 2016, a new Category I CPT code became effective for Cologuard; 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 a positive or negative result.”\textsuperscript{29} Cologuard is the only sDNA test currently available in the United States that fits the long description, 81528 is specific for Cologuard at the present time. Category I codes are only assigned to products that have FDA approval, are widely used by physicians in a manner that is consistent with current medical practice and which have documented clinical efficacy. Specific coding for Cologuard has been in effect since January 1, 2015 when HCPCS Code G0464 was established by CMS.\textsuperscript{30}

In summary, Cologuard is an important addition to the fight against CRC. Cologuard provides an evidence-based, well-validated, noninvasive screening test for CRC and AA and an integrated patient support service that promotes a high test completion rate. It is supported by two large peer-reviewed publications documenting its sensitivity and specificity. It has FDA approval through the rigorous PMA pathway. In addition to being covered by a growing number of commercial health plans, Cologuard is covered through a Medicare NCD, which requires coverage in Medicare Advantage health plans nationwide. Cologuard has achieved coverage of almost one-third of all Americans and over half of the clinically applicable population of Americans over age 50 in less than 18 months. This substantial coverage footprint is compounded by the 17 states and the District of Columbia, representing more than 37% of the U.S. population, that have mandates in place requiring health plans to extend coverage to Cologuard. The ACS and USPSTF have updated their CRC screening guidelines to include Cologuard or mt-sDNA testing. Finally, the cost of Cologuard (US $649) is substantially less than that of colonoscopy.

Extending coverage to Cologuard is an important step toward limiting the burden of CRC. For all the above reasons, health plans should review the data presented in this dossier and consider extending coverage for Cologuard.
REFERENCES


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Cologuard Evidence Shortform Dossier ver. 2.0 (March 1, 2016)
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