Cologuard®: A Call to Action in Colorectal Cancer Screening

Philip Parks, MD, MPH, FACOEM
Senior Director, Head of Medical Affairs
Exact Sciences Corporation

Emily Weiser, MPH
Senior Manager, Medical Affairs
Exact Sciences Corporation
Executive Summary

Cologuard® is a comprehensive, patient-centered colorectal cancer (CRC) screening solution developed by Exact Sciences with a proven ability to detect curable-stage CRC and the most at-risk precancerous lesions. The Cologuard test applies a comprehensive panel of cutting-edge biomarkers coupled with an appealing, patient-centered, at-home test. Cologuard has low barriers to patient adoption and no patient preparation requirements. The single-source laboratory that delivers Cologuard also provides 24/7 patient and provider support through its customer care center, along with highly reliable test analysis, results reporting, and tracking. Cologuard, combined with the Exact Sciences Laboratories services, is a carefully designed CRC screening solution with the potential to substantially reduce CRC as a major public health problem.

The pivotal Multitarget Stool DNA Testing for Colorectal-Cancer Screening (DeeP-C) study was published in the *New England Journal of Medicine* in April 2014.1 The results established the performance and clinical validity of Cologuard and were the basis for its parallel Food and Drug Administration (FDA) and Centers for Medicare and Medicaid Services (CMS) approval in August 2014. Cologuard leverages proprietary stool DNA extraction and detection technology to quantify and analyze eleven distinct biomarkers that identify CRC and precancerous lesions. Cologuard offers the highest sensitivity of all noninvasive tests for curable-stage CRC and precancerous polyps with high-grade dysplasia.1 Cologuard is the only FDA approved, stool-based DNA CRC screening test available to patients aged 50 years and older who are at average risk for CRC.

Nationally recognized guidelines endorse Cologuard as an effective CRC screening solution. Notably, the U.S. Preventive Services Task Force (USPSTF) included Cologuard in its most recent 2016 recommendation statement as an “A” rated preventive service that is equally positioned among other CRC screening strategies.1 The National Committee for Quality Assurance (NCQA) includes Cologuard in their 2017 Healthcare Effectiveness Data and Information Set (HEDIS) quality measures for CRC screening and CMS includes Cologuard in its updated Medicare Advantage Star quality ratings system. Insurance coverage for Cologuard now exists for nearly 90% of the addressable U.S. population, including all Medicare beneficiaries and many commercially insured patients, with no out-of-pocket costs.

Cologuard offers a high patient compliance rate (65%), high sensitivity in detecting CRC (92% across all stages of CRC,1 superior to FIT), and the highest benefits to harms ratio of all other CRC screening modalities.2 Cologuard provides unparalleled patient access through its easy-to-use, noninvasive, at-home test design and widespread insurance coverage. Increasing Cologuard adoption signals a CRC screening paradigm shift as it becomes the preferred solution for a growing number of patients, healthcare providers, and payers. Read this white paper to learn more about how Cologuard is well-positioned to improve CRC screening rates and reduce the human costs related to CRC, the most preventable, but least prevented cancer.4
Cologuard: Reducing the Human Costs of the Colorectal Cancer Screening Gap

Exact Sciences created Cologuard® in collaboration with Mayo Clinic to reduce the human costs due to colorectal cancer (CRC), the fourth most commonly diagnosed cancer in the United States. Cologuard’s proven ability to detect patients with curable-stage CRC and the most at-risk precancerous lesions was published in the New England Journal of Medicine in April 2014. This pivotal Multitarget Stool DNA Testing for Colorectal-Cancer Screening (DeeP-C) study was a prospective, blinded, cross-sectional, multi-center study that enrolled more than 10,000 patients between the ages of 50 and 84 years old from 90 clinical sites. Within months of publication, Cologuard was the first medical product to successfully navigate the joint U.S. Food and Drug Administration (FDA) and Centers for Medicare and Medicaid Services (CMS) parallel review process, receiving premarket approval (PMA) from the FDA on August 11, 2014 and a CMS National Coverage Decision (NCD) on October 9, 2014. As of February 2018, Cologuard remains the only FDA approved multi-target stool DNA test available for CRC screening.

Cologuard is becoming the preferred choice for CRC screening for an increasing number of providers and is well-positioned to become a first-line, standard of care for CRC screening in the United States. Exact Sciences designed Cologuard as a comprehensive, patient-centered CRC screening solution with two complementary components that support successful screening events and demonstrate a commitment to truly “changing the game” in CRC screening. The Cologuard test kit is an easy-to-use, at-home test with no required patient preparation that detects altered DNA biomarkers and hemoglobin from blood in stool samples. Exact Sciences Laboratories was built to be a highly reliable, analytic laboratory with state of the art technology. Today, Exact Sciences Laboratories provides sample processing, as well as a nationwide patient compliance program and provider support 24 hours per day, seven days per week, for each Cologuard test kit.

CRC remains the second most common cause of cancer-related deaths for U.S. men and women combined and poses a significant public health burden due to low, relatively unchanged screening rates. Current guidelines and screening modalities have had limited success in achieving desired CRC screening rates. Each year, more than 135,000 Americans are diagnosed with CRC, and more than 50,000 Americans die from the disease. The National Cancer Institute (NCI) estimates that more than $14 billion per year is spent treating CRC, and projections show this figure will increase annually. According to CMS, the average cost paid by the Federal government per patient death due to CRC is $142,000.

CRC is characterized as the most preventable, but least prevented cancer. Fortunately, CRC and death from CRC are largely preventable with universal, programmatic screening. Patient survival rates improve dramatically when CRC is detected at an early stage. When CRC is detected early (Stage I), the five-year survival rate is more than 90% with surgery alone and typically does not require chemotherapy or radiation. Conversely, the five-year survival rate for Stage IV CRC is 11%. Universal CRC screening programs are recommended in guidelines, but have primarily been an aspirational goal in the battle to reduce CRC morbidity and mortality. Unfortunately, programmatic adherence with CRC guideline recommendations has remained relatively unchanged and U.S. screening rates are disappointingly low, at 62% nationwide (Figure 1). The National Colorectal Cancer Roundtable (NCCRT) 80% by 2018 initiative is joined by more than 1,500 multi-disciplinary organizations committed to achieving a shared goal of an 80% CRC screening rate in adults aged 50 and older by the end of 2018 to substantially reduce CRC as a major public health problem.
Call to Action: Tackling Stagnant Colorectal Cancer Screening Rate

The current CRC screening paradigm does not mirror the standard of care for other cancer screening. CRC screening is unique among other cancer screening in that the most common approach relies on an invasive procedure, colonoscopy, for its most common screening test. CRC is also the cancer with the lowest rate of individuals screened according to guidelines, in stark contrast to screening rates for breast and cervical cancers (Figure 1). As a result, the CRC screening paradigm appears inverted relative to other cancers for which screening is applied (Figure 2). Except in the case of CRC, a noninvasive screening modality is offered first-line for other forms of cancer screening and an invasive procedure, such as colonoscopy, is used for diagnostic purposes following a positive noninvasive screening result.

Patient characteristics, preferences, and test characteristics are important to understand and leverage to increase compliance with CRC screening guidelines. Colonoscopy is an effective diagnostic and therapeutic invasive procedure, but the evidence is clear that population screening with colonoscopy alone has had limited success in achieving desired screening rates. Exact Sciences recognizes that no single CRC screening option alone is capable of achieving desired screening rates. Patients should be informed of CRC screening choices and their associated risks and benefits in a shared decision making discussion with their healthcare provider.

Cologuard's Innovative Advantage

Cologuard is the first and only FDA approved and CMS covered noninvasive, multi-target stool DNA (mt-sDNA) test for CRC screening that combines the analysis of both stool DNA and blood biomarkers into a single patient result. This makes Cologuard an ideal screening solution to address the CRC screening gap and prevent unnecessary human suffering and mortality related to CRC. Since Cologuard’s parallel FDA-CMS review and approval in 2014, insurance coverage has expanded to a level that it now exists for nearly 239 million Americans, including all Medicare beneficiaries and most major commercial insurance companies. Cologuard is covered by Medicare with no out-of-pocket costs to patients, and positive medical policies and/or coverage for Cologuard has been secured for nearly 90% of the addressable U.S. population. The Affordable Care Act stipulates that because Cologuard is considered a preventive service, it should be covered by most insurance plans with no out-of-pocket cost to patients by June 2018. Cologuard is available by prescription for adults aged 50 years and older at average risk for CRC.
As of January 2018, more than 102,000 healthcare providers have ordered Cologuard and more than 923,000 Cologuard tests have been completed. Patient compliance with Cologuard screening through December 2017 was 65%, exceeding reported figures for fecal immunochemical tests (FIT) and colonoscopy, and 48% of a sample of patients screened with Cologuard in 2017 reported they have never been screened for CRC prior to using Cologuard (Figure 3). This high patient compliance rate reflects the systematic approach to screening that the Exact Sciences 24/7 nationwide patient compliance program and customer care center provide. The Cologuard compliance rate is two to four times greater than the compliance rate with other stool-based CRC screening modalities and nearly 75% greater than published compliance rates with colonoscopy.

Cologuard Detects Cancer and Precancerous Lesions

Cologuard leverages proprietary stool DNA extraction and detection technology to quantify and analyze eleven distinct biomarkers that identify CRC and precancerous lesions. Figure 4 graphically illustrates the biological processes associated with cellular exfoliation (or “shedding”) of methylated or altered DNA into stool. Precancerous polyps and cancerous lesions continuously shed altered DNA biomarkers into stool, and blood can be released into stool either intermittently or continuously. In addition to detecting altered DNA biomarkers, the Cologuard test includes an embedded FIT test to enhance overall assay performance and detect hemoglobin from blood in stool samples. FDA approved and proprietary Quantitative Allele-specific Real-time Target and Signal Amplification (QuARTSTM) assays and an Enzyme-Linked Immunosorbent Assay (ELISA) hemoglobin assay provide a combined analytical test result from the altered DNA and blood-based biomarkers in each stool sample. A single qualitative, positive or negative, test result is reported based on the composite score from the quantitative values of all eleven biomarkers present in the stool sample. A “positive” result may indicate the presence of CRC or advanced adenomas and should be followed by a diagnostic colonoscopy.
Cologuard: Easy for Patients and Healthcare Providers

Cologuard uses a stool sample collected in the privacy and comfort of a patient’s home. The test does not require any bowel preparation or changes to diet or medications.

Healthcare providers can order Cologuard by fax, e-fax, an Exact Sciences online ordering portal, or through electronic health record systems. After receiving an order, the Exact Sciences Laboratories’ 24/7 patient compliance program reaches out to each patient through its customer care center to answer any questions. Exact Sciences Laboratories ships the test kit (Figure 5) to each patient’s home, which includes everything the patient needs to collect their sample: an instruction booklet in English and Spanish, a sample collection container, a support bracket that rests on their toilet, a fecal hemoglobin sample tube, a buffer solution for DNA stabilization during sample transport, and a pre-paid return shipping label. Patients can collect their sample whenever it’s most convenient for them and then place their sample back into the sample collection kit. Next, patients can leave the complete kit on their doorstep and arrange for a pre-paid pick-up at their home, or return their completed kit to a drop-off station for transport to Exact Sciences Laboratories. A return office visit to a patient’s healthcare provider is not required to process their sample. The sample is transported to Exact Sciences Laboratories, where highly reliable processes and standard operating procedures ensure that each sample is properly processed, analyzed, and resulted. Results are reported directly to the ordering healthcare provider who then communicates the result to their patient.

Cologuard: Included in Major Guidelines and Quality Measures

Nationally recognized guidelines endorse Cologuard as an effective screening test for CRC. Effective June 2016, the U.S. Preventive Services Task Force (USPSTF) determined that CRC screening for patients aged 50-75 years was an “A” rated process. The USPSTF included Cologuard in this recommendation statement as one of several equally positioned “A” rated strategies for CRC screening. “A” rated strategies are included in the prevention benefit of the Affordable Care Act to individuals without copays or deductibles. The USPSTF emphasized that “the best screening test is the one that gets done.” Further, the American Cancer Society (ACS) Colorectal Cancer Screening Guidelines (2016) and the National Comprehensive Cancer Network (NCCN) Guidelines (2016) also include the use of Cologuard as a recommended CRC screening modality.

There is convincing evidence that screening for colorectal cancer provides substantial benefit for adults aged 50 to 75 years, and a sizable proportion of the eligible US population is not taking advantage of this effective preventive health strategy. With this recommendation, the USPSTF acknowledges that there is no “one size fits all” approach to colorectal cancer screening and seeks to provide clinicians and patients with the best possible evidence about the various screening methods to enable informed, individual decision making.

- United States Preventive Services Task Force, June 2016
Based on modeling studies, as recommended by the Agency for Healthcare Research and Quality (AHRQ), an initial Cologuard re-screening interval of three years is included in nationally recognized guidelines from the USPSTF, ACS, and the NCCN. CMS has approved reimbursement for a re-screening interval of three years and the USPSTF guidelines recommend an interval of either one or three years. Insurers that include Cologuard as a covered benefit cover the test every three years.

The National Committee for Quality Assurance (NCQA) includes Cologuard in their 2017 Healthcare Effectiveness Data and Information Set (HEDIS) quality measures for CRC screening. The inclusion of Cologuard in the NCQA HEDIS metrics allows payers, health systems, and providers the opportunity to receive quality credit in the form of financial reimbursements for any Cologuard tests performed during a three-year lookback period. For example, for the 2017 HEDIS audit, 2016 performance using these quality measures will give credit for completed Cologuard tests beginning in 2014, when Cologuard received FDA approval and was made available to patients. Effective April 2017, CMS included Cologuard in its updated Medicare Advantage Star Ratings program, meaning Medicare Advantage plans can increase their Star Ratings when their beneficiaries complete Cologuard. Cologuard’s inclusion in the Medicare Advantage Star Ratings program creates consistency with the HEDIS quality ratings. Medicare Advantage plans will now receive quality credit for Cologuard tests completed in 2014 and beyond, and these updates could have a positive impact on the overall Star Ratings of Medicare Advantage plans. Both the HEDIS and Stars programs offer strong economic incentives for payers, health systems, and providers to improve CRC screening rates and other quality metrics.

Cologuard: Proven Clinical Validity and Clinical Utility

A substantial and growing body of evidence published in the peer-reviewed scientific literature supports the Cologuard CRC screening solution. In 2014, the results of a 10,000 patient pivotal study (DeeP-C) were published in the New England Journal of Medicine, a preeminent medical and scientific journal. The results of this study established the performance and clinical validity of Cologuard and were the basis for its parallel FDA-CMS approval.

**Figure 6: Sensitivity Comparison: Cologuard versus FIT**

<table>
<thead>
<tr>
<th>Point Sensitivity</th>
<th>CRC I-IV</th>
<th>CRC I-II</th>
<th>HGD</th>
<th>SSP</th>
<th>AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>mt-sDNA</td>
<td>92%</td>
<td>94%</td>
<td>69%</td>
<td>42%</td>
<td>42%</td>
</tr>
<tr>
<td>FIT</td>
<td>74%</td>
<td>70%</td>
<td>46%</td>
<td>5%</td>
<td>24%</td>
</tr>
</tbody>
</table>


CRC I-IV = colorectal cancer, any stage, as defined by the American Joint Committee on Cancer (AJCC)
CRC I-II = colorectal cancer, stages I-II, as defined by the American Joint Committee on Cancer (AJCC)
HGD = high-grade dysplasia
SSP = sessile serrated polyps measuring 1 cm or greater
AA = advanced adenomas measuring 1 cm or greater

DeeP-C was a prospective, blinded, cross-sectional, multi-center study that enrolled over 10,000 patients between the ages of 50 and 84 years from 90 clinical sites in the United States and Canada. The study results demonstrate that Cologuard has an overall 92% sensitivity and 87% specificity for all stages of CRC, and notably a sensitivity for curable-stage cancers (Stage I-II) of 94% (Figure 6). Compared with the FIT test, Cologuard exhibits significantly greater sensitivity for the detection of CRC and precancerous advanced adenomas, 92% versus 74%, and 42% versus 24%, respectively. Importantly, for adenomas most at risk for progression to CRC, those with high-grade dysplasia, Cologuard was also significantly more sensitive than FIT, 69% versus 46%, respectively. CRC incidence is also progressively right-sided. Currently, about half of all CRC is located on the right side, and conventional screening tools are biased toward left-sided CRC detection. Importantly, Cologuard detection is less affected by tumor site because precancerous polyps and cancerous lesions continuously shed altered DNA biomarkers into stool.
These study results demonstrate that Cologuard is a highly sensitive screening test for CRC with a strong negative predictive value* (NPV) to ensure sound clinical decision making. In comparison with Cologuard, the NPV of FIT does not provide the same level of confidence in deferral of negative results post-screening, particularly for a disease with a significant morbidity and mortality risk when diagnosed in later stages. In DeepC, FIT missed more than three times as many cancers (17/65) as Cologuard (5/65) and five times as many early stage (Stage I-II) cancers (15/50 versus 3/50, respectively).

Cologuard also achieved a high specificity (87%), or 13% false positive rate for patients aged 50-85 years. Cologuard has a specificity of 87% for ruling out cancer and FIT has a specificity of 95%. Cologuard achieved an even higher specificity (91.5%), or an 8.5% false positive rate, for patients aged 50-65 years, which is of high importance to patients, healthcare providers, and commercial health plans with beneficiaries in this age range. Given that the purpose of a screening test is to identify as many patients as possible with early stage and high risk precursors to cancer, sensitivity is the best comparator for the selection of the most appropriate screening test.

Positive Cologuard Results Increase Diagnostic Colonoscopy Yield

Cologuard raises the index of suspicion for gastroenterologists, leading to more productive colonoscopies. This was demonstrated in a Mayo Clinic study\textsuperscript{23} that compared colonoscopic findings and withdrawal times between two groups of patients. The first cohort were patients who underwent a diagnostic colonoscopy at Mayo Clinic after testing positive with a Cologuard screening test; in this group the endoscopist was aware of the Cologuard test result. The second cohort was a group of patients that had a positive Cologuard test result during participation in the DeepC study and their endoscopist was not aware of the Cologuard test result. These patients completed a Cologuard test before undergoing a screening colonoscopy at Mayo Clinic (Rochester, MN; Jacksonville, FL; Scottsdale, AZ). Endoscopists who were aware of the patient’s Cologuard test result found more adenomas (two to one) and their median examination times were nearly 50% longer; 19 minutes for the cohort with the Cologuard results as compared to 13 minutes for the cohort without the Cologuard results. This study demonstrates that an endoscopist’s knowledge of a positive Cologuard test may improve both the yield and quality of the follow-up colonoscopic examination, allowing for a more thorough and accurate inspection of the colon.

Negative Colonoscopy Results Following a Positive Cologuard

Asymptomatic, well-examined, and well-prepared patients with a positive Cologuard result and a negative colonoscopy do not require additional medical testing or clinical evaluation based solely on these “discordant” results.\textsuperscript{24} Based on current guidelines, patients at average risk for CRC with a prior negative colonoscopy should be screened again for CRC at ten years, up to age 75 years. Discordant results are expected and are related to low background levels of methylated DNA and small amounts of fecal hemoglobin, which are present in the stool of all patients. In an expected number of colonoscopy negative individuals, background levels of methylated DNA and fecal hemoglobin are high enough that positive Cologuard tests occur (i.e., a “false positive” result). The Cologuard test and algorithm design account for these background levels by setting the threshold for a positive Cologuard test such that it maximizes CRC detection (sensitivity) with the trade-off of a 13% false positive rate. A long-term study of 379 patients determined to have a false positive Cologuard test result after a negative colonoscopy demonstrated that new cases of aerodigestive cancers were rare and did not exceed incidence estimates in the general population.\textsuperscript{24} These observations are consistent with Cologuard’s FDA Summary of Safety and Effectiveness Data (SSED\textsuperscript{25}) and reinforce that false positive Cologuard test results do not require follow-up evaluations to screen for other types of cancers.

\*Negative predictive value (NPV) is the probability that patients with a negative screening test result truly don’t have the disease of interest, or the percentage of patients with a negative test result who do not have the disease of interest.
Cost, Cost-Effectiveness, and Value of Cologuard

Cologuard Cost and Pricing

Cologuard is approved by CMS for reimbursement at $508.87 as of January 2018 with no out-of-pocket expense for Medicare patients, and many commercially insured patients have access to Cologuard with no out-of-pocket expenses. Out-of-pocket expenses (i.e., copayments, coinsurances, and deductibles) for Cologuard for commercially insured patients are dependent upon specific health plan designs. The Affordable Care Act stipulates that because Cologuard is considered a preventive service, it should be covered by most insurance plans with no out-of-pocket costs to patients by June 2018.

Cologuard is more than a test, it is a CRC screening solution. Cologuard includes a unique test collection kit and shipping costs to and from each patient’s home. Once a patient’s sample arrives at Exact Sciences Laboratories, a sophisticated molecular and immunologic laboratory analysis is completed. Each Cologuard order is also supported by a 24/7 nationwide patient compliance program and customer care center, results reporting and tracking, and longitudinal data warehousing for quality metrics reporting for each provider and patient. No other CRC screening choice (e.g., FIT or colonoscopy) offers 24/7 patient support and a single-source laboratory with highly reliable processing, resulting, and patient reporting.

Cost-Effective Colorectal Cancer Screening Solution

Modeling studies have clearly demonstrated that the cost-effectiveness of Cologuard at three-year intervals is comparable to colonoscopy every ten years.\(^1\) Cost-effectiveness models typically account for benefits (e.g., mortality reduction through detection of cancer in early stages and cancer prevention) and harms (e.g., risks to patients related to complications associated with diagnostic procedures). According to cost-effectiveness modeling requested by the AHRQ, an independent government agency, and the USPSTF, Cologuard at three-year intervals has the highest benefits to harms ratio of all seven USPSTF recommended CRC screening choices.\(^6\) In addition, these models demonstrate that if the Cologuard compliance rate is 70% greater than the compliance rate with FIT, then Cologuard is the most cost-effective CRC screening choice for patients.\(^7\)

The underlying risk driver for patients who undergo CRC screening are the risks associated with invasive and potentially harmful colonoscopy procedures. Cologuard has the highest benefits to harms ratio because modeling studies demonstrate that, at a three-year interval, Cologuard adoption results in the lowest number of colonoscopies of all USPSTF-endorsed CRC screening modalities. Given that CRC and advanced adenomas are only expected to be found in approximately 8%-9% of average risk, asymptomatic screening eligible individuals, the majority of screening colonoscopies in patients at average risk for CRC are negative for advanced lesions.\(^1\) Therefore, in retrospect, an invasive screening colonoscopy procedure is medically unnecessary for the majority of patients at average risk for CRC. Based on modeling studies, broad use of Cologuard in patients at average risk for CRC results in less unnecessary, invasive, and potentially harmful screening colonoscopy procedures.

Cologuard’s Proven Value

In healthcare, “value” is defined by the impact an intervention or screening method has on patient outcomes while accounting for the cost to achieve this outcome.\(^8\) Successful screening occurs when a patient is compliant with his or her screening method of choice. In the case of CRC screening, NCI-sponsored Cancer Intervention and Surveillance Monitoring Network (CISNET) models and other models assume 100% compliance. A key consideration in any “real-world” evaluation of value is whether patients actually complete the healthcare intervention or screening recommendation. Screening test performance is usually optimized for the detection of the disease of interest. When published rates of FIT and colonoscopy compliance, adherence, and performance are taken into account, Cologuard’s cost-effectiveness and value dominate all other CRC screening options with respect to the ratio of benefits to harms.\(^5\) The key differentiator of the Cologuard solution is its high compliance rate combined with high sensitivity (superior to FIT) and the greatest benefits to harms ratio of all other CRC screening modalities.\(^2\)
Cologuard: Closing the Colorectal Cancer Screening Gap

Cologuard offers the potential to improve CRC screening rates with its compelling combination of high sensitivity and specificity in detecting CRC. The Cologuard solution applies a comprehensive panel of cutting-edge biomarkers coupled with an appealing, patient-centered, at-home test with low barriers to patient adoption and highly reliable test analysis, results reporting, and tracking. Cologuard is supported by a nationwide patient compliance program, a critical component of the Cologuard value proposition that results in a high test compliance rate (65%). A study assessing Cologuard use in adults aged 50 to 75 years living in Olmsted County, Minnesota found that Cologuard adoption was highest in those aged 50 to 54 years, a population with only a 49% screening rate, and that colonoscopy decreased for all populations over time while overall CRC screening rates remained steady. Another study assessing Cologuard uptake in a cohort of CRC screening non-compliant, average-risk Medicare patients found an 88.3% Cologuard compliance rate and a 96.1% compliance rate with diagnostic colonoscopy for patients with a positive Cologuard test result.

Effective detection is the most important goal for achieving desired outcomes in screening. Figure 7 highlights how Cologuard compares to other CRC screening modalities by offering a carefully designed CRC screening solution that addresses all elements of the formula for effective detection, including comparatively high:

- Sensitivity for detecting all stages of CRC, including highly-treatable early stage CRC and pre-cancerous lesions
- Patient compliance rates by utilizing a systematic approach to screening, including a 24/7 nationwide patient compliance program and customer care center
- Patient access through widespread insurance coverage and preventive service designation, partnered with patient ease-of-use and a noninvasive, at-home test design

Figure 7: Colorectal Cancer Screening Comparison Chart

<table>
<thead>
<tr>
<th></th>
<th>Cologuard</th>
<th>FIT*</th>
<th>Colonoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Performance</strong></td>
<td></td>
<td></td>
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<tr>
<td>Operator-independent</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Compliance</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Patient compliance program</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Non-invasive</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Avoids bowel preparation</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Avoids missed work</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Can be done at home</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Avoids medication/diet restrictions</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Covered by third parties</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Access</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unlimited (by mail)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

* OC FIT-CHEK, Polymedco
Exact Sciences designed Cologuard as a patient-centered screening choice that also aligns with the goals of healthcare providers, health systems, and health insurance companies. Patient preference factors\textsuperscript{12,32} that drive decisions to participate in CRC screening programs have been accounted for in both the design and implementation of Cologuard, including:

- **Choice** - noninvasive with no medical procedure or sedation required
- **Convenience** - ease of access to testing, patient privacy, no scheduling concerns due to time away from work or other daily activities, and no requirements for bowel preparation, dietary modifications, or changes in medications
- **Performance** - high detection rates of treatable CRC and the highest-risk pre-cancerous lesions
- **Safety** - noninvasive testing process that is inherently safe for patients and has the lowest incidence of harms of all CRC screening options
- **Low impact screening schedule** - three-year testing interval
- **Increased patient awareness** - nationwide, direct-to-consumer advertising

The effectiveness of the Cologuard solution goes even further to support successful screening events with a robust patient compliance program and customer care center. These U.S.-based (Madison, WI) nationwide services directly support each Cologuard patient with the collection and return of their sample. After a healthcare provider prescribes Cologuard, there is timely follow-up with each new provider who orders the test, as well as outreach to all patients from the Exact Sciences Laboratories team. Patients are greeted with a “welcome call” designed to promote a greater understanding of the Cologuard test that is followed by a cascade of activities initiated from the patient compliance program and customer care center, including:

- Patient shipping address is validated
- Sample collection kit is shipped to each patient via overnight delivery
- Reminder calls to patients if the sample collection kit is not returned
- Reminder letter sent via traditional mail if the sample collection kit is not returned

Additionally, the Cologuard customer care center is available 24 hours per day, seven days per week, 365 days per year, to answer questions about the test, sample collection, and shipping details in over 70 languages. These patient compliance and customer care activities support the current Cologuard compliance rate of 65%.\textsuperscript{3} While Exact Sciences is pleased with this relatively high compliance rate to date, we are continuously striving for even higher rates through continuous process improvement of our patient compliance program and customer care center.
Cologuard: Clear Choice over FIT and Colonoscopy

Why Not FIT?

While patient and healthcare provider preference, test cost, and cultural preferences likely play a large role in CRC screening rates, certain characteristics of the available CRC screening tests also contribute to low compliance and adherence nationwide. For example, guaiac fecal occult blood (gFOBT) and FIT tests require yearly testing, which results in poor annual compliance (31%-53%)\textsuperscript{11,16}, only 31% compliance yearly over three years,\textsuperscript{11} and very low year-over-year adherence.\textsuperscript{33} Compared to Cologuard, FIT (OC FIT-CHEK, Polymedco) has a lower sensitivity (74% versus 92%) for CRC overall, early curable-stage CRC (Stage I-II; 70% versus 94%), and high-grade dysplasia (46% versus 69%).\textsuperscript{1} FIT is also poor at detecting a range of precancerous lesions. In particular, FIT misses 95% of sessile serrated adenomas,\textsuperscript{1} which are frequently a right-sided colonic lesion and the cause of up to 30% of colorectal cancers.\textsuperscript{34} While FIT is commonly offered for programmatic CRC screening, the majority of health systems and medical groups lack the infrastructure and resources required to achieve desired annual compliance rates.\textsuperscript{35} As a result, FIT’s “real-world” year-over-year adherence rates are often far less than 30%. In one study, only 0.3% of individuals were found to complete ten consecutive years of FIT testing.\textsuperscript{33} Given FIT’s poor performance (sensitivity for CRC and high-grade dysplasia), including a lower polyp detection rate for sessile serrated and right-sided polyps, need for annual repeat testing, and low compliance rates, FIT is an inferior choice for CRC prevention for most patients, providers, and health systems. Offering FIT to patients without offering Cologuard violates shared decision making principles that should guide informed choices by patients.

FIT is useless for the detection of serrated-class lesions, which account for 20-30 percent of CRC cases, probably because sessile-serrated polyps have few or no surface blood vessels.

- Douglas K. Rex, MD, AGAF
AGA Perspectives, February/March 2017

Why Not Colonoscopy?

Colonoscopy offers the longest CRC testing interval at ten years and has high sensitivity, reported in the modeling literature as high as 95%.\textsuperscript{1} However, screening colonoscopy is an invasive procedure with a risk of significant complications,\textsuperscript{36} is culturally less acceptable to many populations, requires extensive and uncomfortable bowel preparation and time away from work or other activities, is often performed under sedation or anesthesia, requires a healthcare facility, and comes with a high per-procedure cost. These factors and others account for the low nationwide compliance rates for colonoscopy and the relatively stagnant nationwide CRC screening rate. One study found that colonoscopy compliance rates at one year were 38%.\textsuperscript{12} Colonoscopy is subject to significant operator-dependent variability and performance.\textsuperscript{37,38} Adenoma detection rates vary by nearly 10-fold across endoscopists, and detection rates for sessile serrated polyps that are more likely to advance to CRC vary by nearly 20-fold.\textsuperscript{39,40} Low polyp detection rates are associated with a higher likelihood of interval CRC, or cases that occur between every 10-year screening colonoscopy.\textsuperscript{38,39} Rates of complications and hospital visits associated with colonoscopy are estimated to be as high as 4% within 30 days of the procedure,\textsuperscript{36,41,42,43} and healthcare providers and hospitals underestimate these adverse outcomes, in part because patients may seek follow-up care from other providers and facilities.\textsuperscript{44}

CRC screening rates will likely not increase if healthcare providers continue to offer invasive colonoscopy procedures without offering noninvasive, less harmful CRC screening choices, such as Cologuard. In fact, a majority of healthcare providers continue to offer colonoscopy to patients as the only option for CRC screening. Offering procedural or other noninvasive CRC screening options without informing patients about Cologuard is contrary to informed shared decision making, especially given that Cologuard exhibits proven superior clinical performance and compliance advantages over other noninvasive options (e.g., FIT), and has the lowest risk of harms compared to all other CRC screening choices.

\textsuperscript{1}Based on modeling (CISNET) assumptions; there is no high-quality study to validate the sensitivity of colonoscopy.
Cologuard Solution Can Prevent Colonoscopy Over-Screening

Studies suggest that over-screening with colonoscopy is a prevalent issue. Up to 33% of patients may receive a colonoscopy before the ten-year recommended screening interval has elapsed, and a repeat colonoscopy occurs after only 6.9 years, on average.45,46,47 These statistics demonstrate that there are many medically unnecessary, invasive screening colonoscopies being performed, which leads to unnecessary risks to patients. Exact Sciences is able to avoid over-screening or premature screening with Cologuard because the test is provided by a single-source clinical laboratory with a longitudinal patient database. If a patient has been screened using Cologuard and then changes physicians or insurers and receives another Cologuard prescription within the three-year interval, Exact Sciences Laboratories can identify the previous CRC screening event and advise the ordering healthcare provider that the patient is not eligible for Cologuard at that time.

Cologuard: First-Line Choice for Noninvasive Colorectal Cancer Screening

In summary, Cologuard is the only FDA approved, stool-based DNA CRC screening test available to patients aged 50 years and older who are at average risk for CRC. Exact Sciences designed Cologuard as a comprehensive, patient-centered CRC screening solution. Cologuard includes an easy to use, at-home test with no requirements for patient preparation, a 24/7 nationwide patient compliance program and customer care center, and a highly reliable, single-source laboratory with state of the art technology. The Exact Sciences team is committed to truly “changing the game” in CRC screening by providing patient reminders and provider support to achieve best-in-class compliance rates.

"Offering FIT or colonoscopy to patients at average risk for CRC without offering other choices, including Cologuard, goes against shared decision making principles that should guide informed choices by patients.

- David A. Ahlquist, MD
Mayo Clinic, Rochester, MN"
Key Takeaways

Current State of Colorectal Cancer Screening Must Be Changed

- Only 62% of Americans at average risk for CRC are up-to-date with screening
- More than 135,000 Americans are diagnosed with CRC each year and more than 50,000 die unnecessarily from the disease
- When diagnosed early, the survival rate for people with CRC is >90%
- With effective screening, death from CRC can be prevented in the majority of patients
- Every patient deserves the right to choose the best CRC screening option for them

ColoGuard is a Proven Colorectal Cancer Screening Choice for Patients and Healthcare Providers

- High sensitivity, noninvasive test for curable CRC and precancerous polyps with high-grade dysplasia
- More cost-effective than colonoscopy and FIT when compliance rates with ColoGuard are high
- Greatest benefits to harms ratio of the seven USPSTF-recommended CRC screening options
- Not operator dependent (as is the case with colonoscopy) and highly reliable sample analysis
- Nationwide patient compliance program and customer care center
- Easy to use, convenient, at-home test that requires no preparation by patients
- Appealing to patients (nearly 90% satisfaction), especially those who have declined CRC screening in the past or who are previously unscreened
- Covered by Medicare with no out-of-pocket costs and broad-based commercial coverage

Building Momentum for ColoGuard and Exact Sciences

- Ensure that patients, providers, and payers are aware of the ColoGuard solution through medical education, innovative marketing, and sales force investments
- Elevate ColoGuard’s emergence as a first-line CRC screening choice for patients and healthcare providers
- Continue “real-world” validation of the value proposition of ColoGuard’s cost-effectiveness, its impact on unscreened populations, and its appeal to patients and providers
- Develop additional screening and diagnostics technologies to address other leading cancer killers
About Cologuard®

Cologuard was approved by the FDA in August 2014 and results from Exact Sciences’ prospective 90-site, point-in-time, 10,000-patient pivotal trial were published in the *New England Journal of Medicine* in April 2014. Cologuard is indicated to screen adults of either sex, aged 50 years or older, who are at average risk for CRC. A positive result may indicate the presence of CRC or advanced adenomas (AA) and should be followed by a diagnostic colonoscopy. Cologuard is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high-risk individuals. The performance of Cologuard was established in a cross sectional study (i.e., single point in time). Programmatic performance of Cologuard (i.e., benefits and risks with repeated testing over an established period of time) has not been studied. Performance has not been evaluated in adults who have been previously tested with Cologuard. Non-inferiority or superiority of Cologuard programmatic sensitivity as compared to other recommended screening methods for CRC and AA has not been established. False positives and false negatives do occur. Any positive test result should be followed by a diagnostic colonoscopy. Following a negative result, patients should continue participating in a screening program at an interval and with a method appropriate for the individual patient. Cologuard performance when used for repeat testing has not been evaluated or established. For more information about Cologuard, visit www.CologuardTest.com.
References


3Publicly available data from Exact Sciences Corporation. Cologuard® compliance rate from Exact Sciences Laboratories, LLC; data accessed February 20, 2018. Compliance is defined as a patient completing a Cologuard® test within one year of a healthcare provider’s order.


9Exact Sciences Laboratories data, Patient Satisfaction Survey, May-Dec 2017; n = 3,772.


