Introduction

Cologuard Screening for colorectal cancer is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

<table>
<thead>
<tr>
<th>Procedure addressed by this guideline</th>
<th>Procedure code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool-based DNA Colorectal Cancer Screening</td>
<td>81528</td>
</tr>
</tbody>
</table>

What is Cologuard screening for colorectal cancer

Definition

Cologuard® screening test (Exact Sciences) is a proprietary multiple molecular marker assay that measures the presence of certain markers in a stool sample. It is intended to identify people at increased risk for colorectal cancer. It offers an alternative to current screening options.

Colorectal cancer

Colorectal cancer (CRC) is one of the most common types of cancers, with over 135,000 new cases identified each year in the United States. It typically affects adults over 55 years of age, with a median age at diagnosis of 67 years.

Survival rates

Screening programs for CRC allow for its early detection. The earlier CRC is caught, the better chance a person has of surviving. Five year survival rates are 89.8% for localized cancer, 71.1% for cancer that has spread regionally, and 13.8% for CRC with distant metastasis.

Recommended screening

Standard recommended screening for CRC includes guaiac-based fecal occult blood test (gFOBT), fecal immunochemical test (FIT), multitargeted stool DNA test (FIT-DNA), colonoscopy, CT colonography, and flexible sigmoidoscopy.
begins at age 50 years and continues until at least age 75 for people at average risk for CRC.³

Compliance with CRC screening recommendations

Although several screening tests have been endorsed and found to be cost-effective, compliance with CRC screening recommendations is limited. According to 2012 data from the Centers for Disease Control and Prevention (CDC), the percentage of adults over 50 years who reported their CRC screening was up to date ranged from 55.7% to 76.3%, depending on the state.⁴ The CDC estimates that 23 million Americans are not up-to-date on CRC screening.⁵

Test information

Introduction

Cologuard is performed on a stool sample collected at home and sent to the laboratory for analysis. No bowel preparation or dietary or medication restrictions are required to complete the test.¹

Cologuard

Cologuard analyzes 11 molecular markers, including hemoglobin and DNA markers, in the stool sample. Three categories of markers are targeted for testing:¹

• Hypermethylation of the promoter regions of the NDRG4 and BMP3 genes
• Point mutations in the KRAS gene
• Hemoglobin markers, which can be associated with the presence of blood in the colon.

The non-DNA immunochemical assay component used to detect blood is similar to other available Fecal Immunochemical Test (FIT) assays.

Cologuard provides a single, combined result: positive or negative. People who receive positive results should be referred for a diagnostic colonoscopy. Those with negative results can continue with standard CRC screening recommendations.¹

Performance characteristics of the Cologuard assay were determined by a large, prospective multicenter trial (DeeP-C Study) and published by Imperiale and colleagues:⁶

• 9989 participants completed testing and were aged 50-84 years, asymptomatic, and at average risk for CRC. All participants provided a stool sample and underwent diagnostic colonoscopy. The primary outcome was the ability of the Cologuard test to detect CRC.
Sensitivity
- 65 subjects had CRC. 60 of these people had positive Cologuard results, giving a sensitivity of 92.3% for identifying cancer [95%CI: 83.0-97.5].
- 757 had advanced precancerous lesions. 321 of these people had positive Cologuard results, giving a sensitivity of 42.4% for identifying precancerous lesions [95%CI: 38.9-46.0].
- Comparable sensitivities of fecal immunochemical testing were 73.8% and 23.8%, respectively, in this trial.

Specificity
- 9167 subjects had non-advanced adenomas, non-neoplastic findings, and negative results on colonoscopy. 7936 of these people had negative Cologuard results, giving a specificity of 86.6% [95%CI 85.9-87.2].
- If only those with “true negative” colonoscopies are considered, the specificity was 89.8% [95%CI 88.9-90.7].
- Comparable specificities of fecal immunochemical testing were 94.9% and 96.4%, respectively, in this trial.

Guidelines and evidence

Introduction
This section includes relevant guidelines and evidence pertaining to Cologuard screening.

U.S. Preventative Services Task Force
Current CRC cancer screening guidelines from the U.S. Preventative Services Task Force (USPSTF, 2016) recommend the use of gFOBT, FIT, FIT-DNA, colonoscopy, CT colonography, and flexible sigmoidoscopy for individuals ages 50 years to 75 years at average risk of colorectal cancer. For other age groups, the guidelines recommend the following:

- “For older adults aged 76 to 85 years, the benefits of screening for colorectal cancer decline, and the risk of experiencing serious associated harms increases. The most important consideration for clinicians and patients in this age group is whether the patient has previously been screened. Patients in this age group who have never been screened for colorectal cancer are more likely to benefit than those who have been previously screened.”
- “Screening [in adults aged 76 to 85 years] would be most appropriate among adults who 1) are healthy enough to undergo treatment if colorectal cancer is detected
and 2) do not have comorbid conditions that would significantly limit their life expectancy." ³

- “The USPSTF does not recommend routine screening for colorectal cancer in adults 86 years and older. In this age group, competing causes of mortality preclude a mortality benefit that would outweigh the harms.” ³

National Comprehensive Cancer Network

CRC screening guidelines from the National Comprehensive Cancer Network (NCCN, 2019) state the following regarding Cologuard and CRC screening:⁷

- “A combined stool DNA and occult blood test has emerged as a new primary screening tool for CRC. It screens for presence of known DNA alterations during colorectal carcinogenesis in tumor cells sloughed into stool, as well as occult blood... The NCCN panel recommends the use of stool-based DNA/occult blood testing as a screening modality in average-risk individuals, but data to help determine an appropriate interval between screening, adherence to/participation rates of screening, and how stool-based DNA testing may fit into an overall screening program are limited. A screening interval of every 3 years has been suggested and is approved by the FDA.”

- “At 3-year intervals, mt-sDNA [multitarget stool DNA] testing reduced CRC incidence and mortality by 57% and 67% respectively. In addition, there are no or limited data in high-risk individuals; therefore, the use of stool DNA should be individualized. If a result is determined to be a false positive, clinical judgment and shared decision-making should be used.”

- “It is recommended that screening for persons at average risk begin at 50 years of age after available options have been discussed.”

- “Because the risk of colorectal screening increases with age, the decision to screen between ages 76 to 85 years should be individualized, and include a discussion of the risks and benefits based on comorbidity status and estimated life expectancy. The most benefit will likely be seen in individuals who have not been previously screened.”

American Cancer Society

The American Cancer Society, in a 2018 update of their guideline for colorectal cancer screening for average-risk adults, states:⁸

- “The ACS recommends that adults aged 45 years and older with an average risk of CRC undergo regular screening with either a high-sensitivity stool-based test or a structural (visual) examination, depending on patient preference and test availability. As a part of the screening process, all positive results on noncolonoscopy screening tests should be followed up with timely colonoscopy. The recommendation to begin screening at age 45 years is a qualified recommendation.”
• “The recommendation for regular screening in adults aged 50 years and older is a strong recommendation.”
• “The ACS recommends (qualified recommendations) that: 1) average-risk adults in good health with a life expectancy of more than 10 years continue CRC screening through the age of 75 years; 2) clinicians individualize CRC screening decisions for individuals aged 76 through 85 years based on patient preferences, life expectancy, health status, and prior screening history; and 3) clinicians discourage individuals older than 85 years from continuing CRC screening.”

U.S. Food and Drug Administration

The U.S. Food and Drug Administration approved Cologuard through their Premarket Approval (PMA) pathway in August 2014 as an in vitro diagnostic.9

Ongoing trials

• A prospective, longitudinal study (ClinicalTrials.gov identifier NCT02419716) is currently underway to evaluate the impact of repeat Cologuard testing in an average-risk population at three-year intervals.10

• A prospective, observational cohort study (ClinicalTrials.gov identifier NCT02715141), entitled the Molecular Stool Testing for Colorectal Cancer Surveillance (MOCCAS) trial and sponsored by The Netherlands Cancer Institute, is currently recruiting to compare the accuracy of an established molecular stool test (Cologuard) and FIT to colonoscopy for detection of advanced adenomas or colorectal cancer.11

• A prospective, observational cohort study (ClinicalTrials.gov identifier NCT03728348) is currently underway to evaluate the specificity of Cologuard in an average-risk population aged 45 to 49.12

Criteria

Cologuard stool DNA testing may be considered for colorectal cancer screening once every three years when ALL of the following criteria are met:

For ages 45 to 75 years3

• Member has not had any of the following USPSTF recommended (A rating) colorectal cancer screening performed during the recommended screening interval:3
  o Guaiac-based fecal occult blood test (gFOBT) in the past year, or
  o Fecal immunochemical test (FIT) in the past year, or
  o Multitargeted stool DNA test (FIT-DNA) in the past three years, or
  o Colonoscopy in the past ten years, or
CT colonography in the past five years, or
Flexible sigmoidoscopy in the past five years, AND

- No signs or symptoms of colorectal disease, including lower gastrointestinal pain, blood in stool, positive guaiac fecal occult blood test or fecal immunochemical test, AND

- Average risk of developing colorectal cancer defined by the following:
  - No personal history of adenomatous polyps, colorectal cancer, or inflammatory bowel disease, including Crohn’s Disease and ulcerative colitis, and
  - No first degree relative(s) with a diagnosis of colorectal cancer or adenomatous polyps, familial adenomatous polyposis, or Lynch syndrome (hereditary nonpolyposis colorectal cancer), AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy.

For ages 76 to 85 years:

- Member has never been screened for colorectal cancer by any screening method, AND

- No signs or symptoms of colorectal disease, including lower gastrointestinal pain, blood in stool, positive guaiac fecal occult blood test or fecal immunochemical test, AND

- Average risk of developing colorectal cancer defined by the following:
  - No personal history of adenomatous polyps, colorectal cancer, or inflammatory bowel disease, including Crohn’s Disease and ulcerative colitis, and
  - No first degree relative(s) with a diagnosis of colorectal cancer or adenomatous polyps, familial adenomatous polyposis, or Lynch syndrome (hereditary nonpolyposis colorectal cancer), AND

- Member is healthy enough to undergo treatment if colorectal cancer is detected, AND

- Member does not have comorbid conditions that would significantly limit his/her life expectancy, AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy.

For age 86 years and older:

- Routine screening for colorectal cancer is not recommended and therefore not reimbursable.
References
Introduction

These references are cited in this guideline.