FECAL DNA TESTING

Policy Number: CANCER 011.15 T2  Effective Date: May 1, 2017

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Related Policies

- Experimental/Investigational Treatment
- Preventive Care Services

INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting Oxford benefit plans. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members. Oxford reserves the right, in its sole discretion, to modify its policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Clinical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Clinical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Clinical Policy. Other Policies may apply.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

APPLICABLE LINES OF BUSINESS/PRODUCTS

This policy applies to Oxford Commercial plan membership* (see exception below).

*Exception: For New Jersey Commercial plans and products, fecal DNA testing for colorectal cancer screening and/or monitoring IS covered. Precertification is not required.

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBS. However, if such plans choose to provide coverage for benefits which are deemed EHBS, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBS is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.
NON-COVERAGE RATIONALE

Fecal DNA testing for colorectal cancer screening and/or monitoring is unproven and not medically necessary.

There is insufficient published evidence in the clinical literature supporting the diagnostic accuracy of fecal DNA tests to screen for colorectal cancer in asymptomatic, average-risk patients. The gold standard for colorectal cancer screening is optical colonoscopy. There is insufficient published evidence comparing fecal DNA testing to optical colonoscopy. In fact, there is insufficient published clinical evidence that fecal DNA testing reduces the likelihood of mortality from colorectal cancer.

Refer to the policy titled Experimental/Investigational Treatment.

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies may apply.

<table>
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<th>CPT Code</th>
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<td>81528</td>
<td>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</td>
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<tr>
<td>84999</td>
<td>Unlisted chemistry procedure</td>
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DESCRIPTION OF SERVICES

Since prognosis improves dramatically with early detection and treatment, many deaths from colorectal cancer (CRC) might be prevented with the use of widespread screening. A number of diagnostic and screening tests for CRC are available, such as the fecal occult blood test (FOBT), flexible sigmoidoscopy, barium enema and colonoscopy. Some tests identify a precancer state, e.g., colonoscopy, and others identify cancer after it has already developed, e.g., fecal occult blood testing.

Fecal deoxyribonucleic acid (DNA) testing is designed to detect CRC based on the presence of specific, cancer-associated mutations in DNA extracted from stool samples. A positive test result indicates the need for definitive diagnosis via colonoscopy and biopsy. Researchers are investigating next-generation tests that include additional biomarkers, as well as the use of fecal DNA testing as a potential screening tool for other types of gastrointestinal cancers.

CLINICAL EVIDENCE

Meta-analysis was performed to evaluate the diagnostic value of stool DNA (sDNA) testing for multiple markers of colorectal cancer (CRC) and advanced adenoma. A random-effects model was used which included a total of 20 studies identified as eligible (n=5876 patients). Stratification analysis according to risk classification showed that multiple sDNA markers had a high sensitivity and specificity for the high-risk subgroups of both CRC and advanced adenoma but not for the average-risk subgroups of either. Similar findings were true in the methylation subgroup. There was no significant heterogeneity among studies for subgroup analysis. The authors concluded that assessment of multiple markers via the sDNA method has strong diagnostic significance for CRC and advanced adenoma in high-risk individuals, but not in average-risk individuals. Methylation markers appear to have a stronger diagnostic value than mutation markers, especially for premalignant neoplasms. While these results suggest the clinical value of the sDNA diagnostic method, they also reveal the need for large-scale population-based trials to identify precise methylation markers for early stage detection of CRC and adenoma in a general population that includes both high-risk and average-risk individuals, as well as to determine the optimal sDNA test frequency with respect to cost effectiveness (Yang et al. 2013).

Zhang et al.(2014) conducted a quantitative meta-analysis evaluating the accuracy of methylation of genes in stool samples for diagnosing colorectal tumors (n=4484 patients). The sensitivity and specificity for the detection of CRC were 73% and 92%, respectively. For adenoma, the sensitivity and specificity were 51% and 92%, respectively. Pooled diagnostic performance of SFRP2 methylation for CRC provided the following results: the sensitivity was 79% and the specificity was 93%. Additionally, the results of accuracy of SFRP2 methylation for detecting colorectal
adenomas were as follows: sensitivity was 43%, specificity was 94%. Their conclusion was that while showing promise for the accurate detection of CRC, a large number of studies are required to further confirm the role of sDNA for early and accurate CRC diagnosis.

Zhai et al (2016) conducted a meta-analysis designed to evaluate the diagnostic performance of stool DNA testing for CRC and compare the performance between single-gene and multiple-gene tests. Fifty-three studies were included in the analysis (n=7524). The meta-analysis revealed no statistically significant difference between single and multiple-gene tests for detecting CRC. Compared with the single-gene testing, multiple-gene stool DNA testing was shown to confer no better diagnostic performance in the screening of CRC. The high specificity of the assaying stool DNA for CRC-related genes suggested these assays may not only be of benefit to diagnosing CRC but also for evaluation recurrence of the disease. The authors stated that the analysis had several limitations including a heterogeneity patient population as well as most of the included studies were not prospective randomized controlled trials.

A systematic review to assess the available evidence on the validity, diagnostic accuracy and clinical utility of the multitarget DNA test in feces (Cologuard™) for screening for CRC was performed by consulting MedLine, EMBASE and Web of Science to July 2014. Studies on diagnostic tests were selected that evaluated the test in asymptomatic adults who underwent CRC screening. The level of evidence was defined according to the National Institute for Health and Clinical Excellence. A total of 299 literature references were identified including 1 synthesis report and 5 diagnostic test studies. Three of the 5 studies had a case-control design in Sackett phase II and were of moderate quality, and 2 had a prospective design in Sackett phase III and were of high quality. The sensitivity for detecting CRC was greater than 90%, but only 40% for detecting advanced adenomas. The test provided conclusive diagnostic evidence to rule out CRC, although it was not useful for ruling out advanced adenoma. The authors concluded that the Cologuard test is a valid screening test for ruling out cancerous lesions but is suboptimal for ruling out precancerous lesions. There is no evidence in terms of mortality, survival or cost-effectiveness (Onieva-Garcia et al. 2015).

Imperiale et al. (2014) performed a study to evaluate the multitarget stool DNA (sDNA) test as a tool for screening in the detection of both CRC and advanced precancerous lesions. The study included participants (n=9989) at 90 sites and was funded by Exact Sciences. Multitarget stool DNA testing identified 60 of 65 participants with cancer, including 56 of the 60 participants with screening-relevant cancers, for respective sensitivities of 92.3% and 93.3%. Sensitivity did not vary significantly according to cancer stage or location within the colon. Among 757 participants with advanced precancerous lesions, DNA testing detected 321 (42.4%). A total of 69.2% of 39 participants with high-grade dysplasia and 42.4% of 99 participants with sessile serrated polyps measuring 1 cm or larger were identified in DNA testing. The sensitivity of the DNA test was higher for distal advanced precancerous lesions (177 of 325/54.5%) than for proximal lesions (143 of 431/33.2%). Test sensitivity increased as the lesion size increased. The authors concluded that while a stool test combining altered human DNA and fecal hemoglobin showed higher single-application sensitivity than a commercial fecal immunochemical test (FIT) for both CRC and advanced precancerous lesions, downstream effects of these factors on outcomes (including both cause-specific and overall morbidity and mortality) require further study.

The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review of the evidence on fecal DNA testing to screen for CRC. The report concluded that there is insufficient evidence about the diagnostic accuracy of fecal DNA tests to screen for CRC in asymptomatic, average-risk patients. There is also insufficient evidence for the harms, analytic validity and acceptability of testing in comparison to other screening modalities. Existing evidence has little or no applicability to currently available fecal DNA testing (Lin et al., 2012).

Ahliquist et al. (2012) assessed colorectal neoplasm detection by a next-generation stool DNA (sDNA) test. The authors performed a blinded, multicenter, case-control study using archived stool samples from 252 patients with CRC, 133 with adenomas ≥1 cm and 293 individuals with normal colonoscopy results (controls). The sDNA test identified 85% of patients with CRC and 54% of patients with adenomas ≥1 cm with 90% specificity. The test had a high rate of detection for all nonmetastatic stages of CRC. Detection rates increased with adenoma size: 54% ≥1 cm, 63% >1 cm, 77% >2 cm, 86% >3 cm, and 92% >4 cm. The authors concluded that early-stage CRC and large adenomas can be detected throughout the colorectum and with higher levels of accuracy by the sDNA test. Neoplasm size, but not anatomical site, affected detection rates. Further studies are needed to validate the findings in a larger population and optimize the sDNA test.

The National Cancer Institute (NCI) states there are no data from RCTs on the effect of other screening interventions (i.e., fecal occult blood test combined with sigmoidoscopy, barium enema, colonoscopy, computed tomographic colonography, and stool DNA mutation tests) on mortality from CRC (NCI, 2016).

The National Comprehensive Cancer Network (NCCN) recommends the use of stool-based DNA/occult blood (OB) 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 rescreening interval of every 3 years has been suggested and is approved by
the FDA. Because there are no or limited data in high-risk individuals, the use of stool-based DNA/OB testing should be individualized. If a result is determined to be a false positive, clinical judgment and shared-decision making should be used (NCCN, 2016).

In 2015, the U.S. Preventive Services Task Force (USPSTF) recommendation on screening for CRC concluded that evidence remained insufficient to assess benefits or harm for fecal DNA testing as a screening modality for CRC. In the 2016 statement, the USPSTF does not take a position on benefits or harm for any screening strategies (e.g., stool-based tests or direct visualization tests). Instead, their emphasis is on the importance of CRC screening for adults aged 50 to 75 years versus the specific screening approach.

**Professional Societies**

**American Cancer Society (ACS)**

The ACS recommends one of the screening tests below starting at age 50 for both men and women at average risk for CRC (2016). If a screening test result is positive, colonoscopy should be performed:

- **Tests that find polyps and cancer**
  - Flexible sigmoidoscopy every 5 years
  - Colonoscopy every 10 years
  - Double-contrast barium enema every 5 years
  - CT colonography (virtual colonoscopy) every 5 years

- **Tests that mainly find cancer**
  - Guaiac-based fecal occult blood test (gFOBT) every year
  - Fecal immunochemical test (FIT) every year
  - Stool DNA test every 3 years

**American College of Gastroenterology (ACG)**

ACG guidelines for colorectal cancer screening state that annual Hemoccult Sensa and fecal DNA testing every 3 years are alternative cancer detection tests. However, because of more extensive data (compared with Hemoccult Sensa), and the high cost of fecal DNA testing, the ACG recommends the fecal immunochemical testing (FIT) as the preferred cancer detection test (Grade 1B – strong recommendation, moderate-quality evidence) (Rex et al., 2009).

**American College of Physicians (ACP)**

The ACP recommends average-risk adults aged 50 to 75 years should be screened for CRC by 1 of 4 strategies:

1. Annual high-sensitivity guaiac-based fecal occult blood test (gFOBT) or fecal immunochemical test (FIT),
2. Flexible sigmoidoscopy every 5 years,
3. High-sensitivity gFOBT or FIT every 3 years plus flexible sigmoidoscopy every 5 years, or
4. Colonoscopy every 10 years.

Regarding DNA stool tests, more comparative effectiveness data are needed (Wilt et al. 2015).

**American Academy of Family Physicians (AAFP)**

In its Clinical Preventive Service Recommendation for Colorectal Cancer Screening in Adults (2016), the AAFP concludes that the evidence is insufficient to assess the benefits and harms of fecal DNA testing as a screening modality for CRC.

**Canadian Task Force on Preventive Health Care**

The group recommended that adults aged 50 to 59 years (weak recommendation) and 60 to 74 years (strong recommendation) be screened for CRC with gFOBT or FIT every 2 years or flexible sigmoidoscopy every 10 years. It recommended against screening in adults 75 years and older (weak recommendation) and against using colonoscopy as a primary screening test (weak recommendation) (2016.)

**U.S. FOOD AND DRUG ADMINISTRATION (FDA)**

On August 11, 2014, the U.S. Food and Drug Administration approved Cologuard, the first stool-based colorectal screening test that detects the presence of red blood cells and DNA mutations that may indicate the presence of certain kinds of abnormal growths that may be cancers such as colon cancer or precursors to cancer. Additional information available at: [https://www.accessdata.fda.gov/cdrh_docs/pdf13/p130017a.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf13/p130017a.pdf). (Accessed April 4, 2017)
REFERENCES

The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealthcare Medical Technology Assessment Committee. [2017T0383Q]


POLICY HISTORY/REVISION INFORMATION

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<td>05/01/2017</td>
<td>• Updated supporting information to reflect the most current clinical evidence and references; no change to coverage rationale or list of applicable codes</td>
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