The FDA has approved Cologuard (Exact Sciences), a stool DNA test, to screen average-risk adults ≥50 years old for colorectal cancer.

COLORECTAL CANCER SCREENING — Conventional screening for colorectal cancer includes noninvasive and invasive tests. Fecal immunochemical tests (FITs) for occult blood have largely replaced guaiac-based tests for noninvasive screening. Invasive options include double-contrast barium enema, flexible sigmoidoscopy, colonoscopy, and computed tomography colonography (“virtual colonoscopy”). Multiple guidelines recommend screening average-risk patients with colonoscopy beginning at age 50 and repeating every 10 years. The American College of Gastroenterology recommends that screening begin at age 45 for African Americans. When colonoscopy is not available or the patient declines the procedure, guidelines recommend screening with flexible sigmoidoscopy every 5 years and/or fecal occult blood tests annually. Some guidelines now recommend computed tomography colonography every 5 years as another alternative for average-risk patients.

THE NEW TEST — The stool DNA test includes molecular assays for DNA mutation and methylation biomarkers associated with colorectal neoplasia (KRAS mutations and NDRG4 and BMP3 methylation) and a non-DNA immunochemical assay for human hemoglobin that is almost identical to the assay used in FITs. A reference gene (Beta-actin) for the estimation of the total amount of human DNA present in each sample is also included. The results of the mutation, methylation, and hemoglobin assays are combined to produce a composite score that is then compared to a cutoff value to determine a positive or negative result.

CLINICAL STUDY — A clinical study in asymptomatic persons ≥50 years old at average risk for colorectal cancer compared the stool DNA test with a FIT (OC FIT-CHEK), each performed on the same stool sample. All participants also underwent screening colonoscopy as the reference standard. Out of 9989 patients, 65 had colorectal cancer and 757 had advanced precancerous lesions detected on colonoscopy.

The sensitivity for detecting colorectal cancer was 92.3% with the DNA test (60 of 65) and 73.8% (48 of 65) with FIT. (A recent meta-analysis indicates that the sensitivity of FITs varies with the assay cutoff value for a positive test result; at the lowest cutoff value, the sensitivity of FITs was 89%.) The sensitivity for detecting advanced precancerous lesions was 42.4% (321 of 757) with the DNA test and 23.8% (180 of 757) with FIT. Both differences were statistically significant. The DNA test identified 42.4% of serrated sessile polyps >1 cm; FIT detected only 5.1% of these lesions.

Among 9167 subjects with either non-advanced adenomas or negative results on colonoscopy, 1231 had positive findings with the DNA test compared to 472 with FIT, resulting in specificities of 86.6% and 94.9%, respectively. Among 4457 participants with only negative findings on colonoscopy, the specificity of the DNA test was also lower than that of FIT (89.8% [455 positive] vs. 96.4% [162 positive]).

ADMINISTRATION AND COST — As with FIT, use of Cologuard requires the patient to collect a single stool sample, and there are no dietary or medication restrictions. The Cologuard collection kit is shipped directly to the patient’s home. It contains written instructions, a bracket and a sample container that are placed on the toilet to collect the stool sample, a separate tube for collection of part of the sample for hemoglobin testing, a bottle of liquid preservative that is poured into the sample container, and a shipping box and labels. Patients send the sample back to the laboratory, which must receive it within 72 hours of collection. A positive result should be followed by a diagnostic colonoscopy.
How often patients should be screened with the Cologuard test has not been established. The manufacturer has suggested once every three years and the Centers for Medicare and Medicaid Services (CMS) is proposing coverage for that interval. According to the manufacturer, the Cologuard test costs $599. The Medicare reimbursement rate for FITs is about $23.

CONCLUSION — One-time screening with a new stool DNA test (Cologuard) detected 92% of cases of colorectal cancer in asymptomatic average-risk persons, but it detected less than half of advanced precancerous lesions and produced a substantial number of false-positive results.