Clinical Practice Assessment

Stool DNA Testing for Colorectal Cancer Screening (Cologuard)

Clinical Question: Is the negative predictive value of the Cologuard stool DNA test for colorectal cancer high enough to avoid colonoscopy if the Cologuard is negative?

Bottom Line: The negative predictive value (NPV) of the Cologuard stool DNA test for colorectal cancer was 99.9% in the pivotal DeeP-C trial that evaluated 9989 participants. The NPV of Fecal Immunochemical Testing (FIT) was 99.7%. While there are more false negative results with FIT compared with Cologuard, the low prevalence of the disease results in little difference in NPV between the two tests. The current retail cost of Cologuard is $599, compared with $22 for FIT.

The Cologuard and FIT were less sensitive in detecting advanced precancerous lesions, hence are recommended more frequently than colonoscopy (Cologuard every 3 years; FIT annually).

Synopsis: The USPSTF considers the following essential components of a screening strategy: (1) the condition must be sufficiently common and important to warrant screening; (2) the condition must have an asymptomatic phase allowing for early detection and treatment; (3) reliable and acceptable detection method(s) must be available; (4) treatment in the asymptomatic phase must yield superior results compared to treatment during the symptomatic phase; and (5) the magnitude of the benefit from treatment in the asymptomatic phase must outweigh the harms of early detection and treatment.

Colon cancer fulfills these criteria. Colonoscopy is the gold standard screening technique. Unfortunately colonoscopy is invasive, expensive, requires bowel preparation that is inconvenient, and is not readily available in all communities. The CDC has estimated that only 1/3 of eligible adults in the US receive colonoscopy screening as recommended. Other screening modalities include fecal occult blood testing and fecal immunochemical testing (FIT). Also see CPA on fecal occult blood testing: [http://www.deancare.com/providers/patient-care/sgbp/cpa/#fobt](http://www.deancare.com/providers/patient-care/sgbp/cpa/#fobt)

The Cologuard test analyzes stool for the presence of hemoglobin and DNA markers, which may indicate the presence of colorectal cancer or advanced adenomas. The test requires a single stool sample without any dietary restrictions. Based on the combined results of all the selected DNA markers and hemoglobin, a single qualitative Cologuard result, positive or negative, is determined.

In the pivotal DeeP-C trial, 12,776 participants aged 50 to 84 considered to be at average risk for colon cancer were enrolled at 90 sites (1). Exclusion criteria included personal history of colorectal neoplasia; digestive cancer; inflammatory bowel disease; colonoscopy within the previous 9 years; barium enema, CT colonography or sigmoidoscopy within the previous 5 years; positive fecal occult blood testing within the previous 6 months; past history of colorectal resection for any reason other than sigmoid diverticula; overt rectal bleeding within the previous
30 days; personal or family history of colorectal cancer. Of the 12,776, 9989 had results that could be fully evaluated. All had colonoscopy, Cologuard, and FIT testing (see Table 1). 65 participants were diagnosed with colon cancer on colonoscopy. Of these, the Cologuard was positive in 60, negative in 5 yielding a negative predictive value of 99.9%. FIT was positive in 48, negative in 17 yielding a negative predictive value of 99.7%. Colonoscopy revealed 758 participants with advanced precancerous lesions. Cologuard was positive in 321 of these, FIT was positive in 180.

4457/9989 participants had entirely negative results on colonoscopy. Of those, Cologuard was positive in 455. FIT was positive in 162. Consequently a positive Cologuard does not necessarily correlate with the presence of colon cancer.

On August 11, 2014 Cologuard became the first product reviewed through a joint FDA-CMS pilot program known as parallel review where the agencies concurrently review medical devices to help reduce the time between the FDA’s approval of a device and Medicare coverage.

CMS proposes to cover the Cologuard test once every three years for Medicare beneficiaries who meet all of the following criteria:

- Age 50 to 85 years, asymptomatic (no signs or symptoms of colorectal disease including but not limited to lower gastrointestinal pain, blood in stool, positive guaiac fecal occult blood test or fecal immunochemical test)
- Average risk of developing colorectal cancer (no personal history of adenomatous polyps, of colorectal cancer, or inflammatory bowel disease, including Crohn’s Disease and ulcerative colitis; no family history of colorectal cancers or an adenomatous polyp, familial adenomatous polyposis, or hereditary nonpolyposis colorectal cancer).

The current retail costs of Cologuard and FIT are $599 and $22 per sample respectively.

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GI Statement: Cologuard for Colon Cancer Screening.

The FDA approved Cologuard (Exact Sciences) in August 2014 as novel method for colorectal cancer screening. Due to the substantial media attention and marketing, patients and physicians have been asking about its role in colorectal cancer screening. Despite the excitement, whether this test will reduce colorectal cancer mortality remains unproven and therefore its place alongside the two existing major screening strategies, colonoscopy and fecal immunohistochemical testing (FIT), remains quite uncertain.

Occult blood testing.

FIT testing is a refinement of guaiac-based stool testing that has been shown to be effective in reducing colon cancer mortality. In the Minnesota Colon Cancer Study, a 17% reduction in colon cancer incidence and a 33% reduction in colon cancer deaths were achieved. In order to achieve this benefit, however, participants returned stool samples annually for 10 years (Mandel, NEJM 1993). ANNUAL repetition is important since all stool tests remain poor at detecting precancerous polyps. BIENNIAL screening in this study provided only a 21% mortality benefit (Mandel, JNCI 1999).

In actual practice, a smaller percentage of patients comply with annual screening. Fewer than half of patients are compliant after 2 years and compliance rates closer to 20-30% are often reported. FIT screening is expected to only reduce colon cancer mortality by 15-20% compared with the 53-67% mortality reductions seen with colonoscopy in large case-control trials (Young, J Cancer 2013).

Cologuard.

Cologuard is a stool based colon cancer screening test. Two stool samples are collected and mailed back to the company. One sample is analyzed for blood and the other for DNA mutations associated with colon cancer. Its approval was based largely on the results of the DEEP-C study, a multicenter trial of 10,000 patients who underwent screening with Cologuard, FIT, and colonoscopy (Imperiale, NEJM 2014). The results showed:

- Cologuard detected 92% of cancers compared with 74% with FIT.
- 42% of advanced adenomas (polyps > 1 cm) compared with 24% with FIT.
- False positive rate was 13% compared with 5% with FIT.

The test is sold for $600 and it is recommended that patients be screened every 3 years.

What test to choose for initial screening?

Although Cologuard is marketed as a non-invasive alternative to colonoscopy, the test is unlikely to PREVENT colon cancer, rather it is a fairly effective method to DETECT colon cancer. It might be more effective than FIT at detecting colon cancer at an early and possibly curable stage due to its improved sensitivity (92% v. 74% in their study). Non-compliance with all stool based testing remains a concern.
Since FIT is performed annually versus Cologuard every 3 years, the sensitivity in actual practice is hard to predict and therefore it may not achieve the 30% mortality reduction seen with FIT in the optimal setting.

Additionally, due to the lower specificity that FIT, more than one in ten patients will receive a result suggesting that they have colon cancer and will require colonoscopy. Over 10 years (three Cologuard testing cycles) the false positive rate may be as high as 1 in 5.

Finally given the cost of FIT v. Cologuard ($24 versus $600), annual FIT testing may still be the dominant screening strategy for patients wishing to forgo colonoscopy.

**What should we tell our patients?**

- Cologuard is likely inferior to colonoscopy at detecting and PREVENTING colon cancer and colonoscopy remains the best option for colon cancer screening.
- For patients who decline colonoscopy, stool testing remains a viable alternative.
- Cologuard is an improvement on stool FIT testing, but it is costly and has a higher false positive rate.
- For patients wishing to AVOID colonoscopy FIT testing might still be a better alternative due to a much lower false positive rate.
- Major groups such as the US Preventative Task Force have not yet weighed in the value of this test and many insurance companies have not decided whether to cover this.

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