Context

In Canada, two different types of fecal occult blood tests (FOBTs) are used for noninvasive colorectal cancer (CRC) screening: the traditional guaiac-based FOBT and the newer fecal immunochemical (blood) test (FIT).\(^1\) FOBTs detect hidden (occult) blood in stool, which may be an indicator of CRC, bleeding polyps (a precursor to CRC), or other gastrointestinal diseases. Each of these modalities has limitations regarding sensitivity and/or specificity, and they are associated with less than optimal compliance rates. As well, high costs of follow-up for false-positive results have caused concern.\(^1\)

These limitations have triggered many innovations in stool testing, particularly for tests that provide greater convenience, are noninvasive, and offer the potential to boost CRC screening rates and subsequently reduce burden of disease. Recent advances in the sequencing of the human genome and the development of high-throughput molecular techniques have accelerated the development of fecal deoxyribonucleic acid (DNA) testing for CRC, a novel screening test that has shown particular promise.

Objective

The purpose of this report is to investigate the status of fecal DNA tests as emerging technologies, and the potential role of these tests as CRC detection tools in average-risk screening populations.

Results of this report are based on a limited literature search and communications with key informants. As such, the comprehensiveness of this report cannot be guaranteed. This report is based on information gathered as of May 2010.

Results

About the test

The fecal DNA test is an alternative, noninvasive CRC screening tool. It can detect DNA mutations that are characteristic of some types of cancerous tumours and precancerous polyps. The test is intended to provide improved sensitivity and/or specificity and, due to ease of use, incentive for better compliance.

The fecal DNA is intended as a first-line screening tool for colorectal cancer in asymptomatic individuals or as a monitoring tool in patients with known or suspected hereditary nonpolyposis colorectal cancer.\(^2\)

The test requires a single, whole bowel movement for analysis. Individuals are expected to collect the bowel movement in a special container and send the package to a laboratory for analysis. Results are made available within three to six weeks.\(^3\)

The laboratory evaluation identifies specific genes using polymerase chain reaction (PCR) analytic methodologies.\(^4\) Genetic alterations in the genes may indicate the presence of precancerous polyps or colon cancer.\(^4\) If the test is positive, a follow-up colonoscopy is necessary to evaluate the presence of lesions and remove any polyps.\(^4\)

The recent discovery that DNA hypermethylation occurs more frequently in CRC than previously believed has galvanized the development of a new generation of cancer biomarkers. There is a general lack of consensus, however, on how many or which markers are necessary to achieve optimal sensitivity. Several combinations of markers in early stool assays have produced high detection rates of both CRC and advanced adenomas in selected patient groups, but
observations from large representative populations are currently lacking.\textsuperscript{5,6}

Improvements in next-generation fecal DNA tests include the use of stool preservatives, more discerning markers, and more technologically advanced and sensitive analytical techniques, such as digital melt curve (DMC) assay and methyl-BEAMing (beads, emulsion, amplification, magnetics).\textsuperscript{6} The former analytic technique quantifies low-abundance mutations in stool samples, and the latter one enables absolute quantification of the number of methylated molecules in a sample, and can detect as few as one methylated molecule in approximately 5,000 unmethylated molecules in DNA from fecal (as well as blood) samples.\textsuperscript{6,7}

The main benefits of this test over the commonly used FOBT and FIT include:\textsuperscript{5}
- since DNA is continuously released into the feces, only a single stool sampling is required rather than multiple stools per screen
- specificity is enhanced as DNA is shed continuously and not intermittently (as seen with blood)
- colonocyte exfoliation is more abundant in cancers than normal mucosa, enhancing the test’s sensitivity
- DNA is relatively stable during transportation and storage of stool samples
- newer methodologies have the capability of detecting a signal from the DNA of a small number of cancer cells
- no diet or medication restrictions are required
- the test could potentially reduce screen frequency because of its capacity to detect precursor lesions.

The main concerns of this test include:\textsuperscript{8}
- verifying the optimal interval between screening tests with stool DNA, which is still uncertain due to the lack of longitudinal follow-up
- determining if false-positive rates can be maintained appropriately low for a screening program
- establishing which patients should not be screened with fecal DNA testing
- ascertaining whether or not sensitivity for large adenoma can be significantly increased compared with FOBT
- verifying if the test improves compliance with CRC
- demonstrating whether or not the test is cost-effective
- performance of new versions of the test, which are unknown.

Fecal DNA tests have also shown promise as noninvasive methods to detect gastric cancers. Potential expanded applications of stool DNA testing include detection of supracolic aerodigestive cancers and of dysplasia in inflammatory bowel disease.\textsuperscript{9}

Who might benefit
Noninvasive tests are intended as screening interventions for average-risk candidates. Average-risk candidates include those between the ages of 50 and 74, with no family or personal history of CRC. There are approximately seven million people in this age range in Canada who would be potentially eligible for primary screening for CRC.\textsuperscript{10}

Evidence
Two recent studies have validated the sensitivity and/or specificity of newer DNA fecal tests. In 2009, Zou\textsuperscript{11} et al. conducted a fecal DNA testing study using the novel DMC assay. The assay was found to have a high level of sensitivity in identifying patients with colon cancer. The DMC assay was also found to be better than standard fecal screening methods in identifying patients with advanced adenomas. In 2008, Itzkowitz\textsuperscript{12} et al. conducted a study to determine whether second generation fecal DNA tests that utilized two markers, the hypermethylated vimentin gene, and a two-site DNA integrity assay showed a higher sensitivity for CRC. The study found that the second-generation test shows higher sensitivity (83\%) and higher specificity (82\%) for CRC than first-generation versions. And, the use of two markers made the test easier to perform, reduced the cost, and facilitated distribution to local laboratories.
In 2008, Ahlquist et al. published results of a seven-year multicentre study using fecal DNA tests. The study assessed the relative potential of a new fecal DNA test compared with the standard FOBT and an older fecal DNA test. The study population included 3,800 asymptomatic participants considered to be at average risk of developing CRC. The study found that the newer fecal DNA test was twice as effective at detecting cancer and serious precancerous polyps than either current blood stool sample tests or an older version of fecal DNA tests.

A multicentre prospective study published in 2004 by Imperiale et al. compared fecal DNA and FOBT tests. The study involved 5,486 participants, all average-risk adults over 50 years of age. Each patient underwent a complete evaluation including fecal DNA analysis, FOBT, and colonoscopy. Fecal DNA sensitivity for cancer was found to be four times that of FOBT. For advanced adenoma with high-grade dysplasia, fecal DNA sensitivity was more than two times that of FOBT. However, neither of these noninvasive screening tests approached the accuracy of colonoscopy, which identified nearly twice as many cases of CRC.

The percentage of noncompliant participants in this study was 12% for the fecal DNA test and 8% for the FOBT. In contrast, a follow-up questionnaire returned by 84% of all participants indicated a 45% preference for the fecal DNA test, as compared to 32% for the FOBT and 15% for colonoscopy.

Cost-effectiveness

A 2007 incremental cost-effectiveness analyses that compared first-generation versions of fecal DNA tests with currently recommended CRC screening strategies found that none of the fecal DNA tests had a cost-effectiveness advantage over the recommended screening tests. The investigators concluded that only if significant improvements for the fecal DNA test characteristics or relative adherence with the fecal DNA testing compared with other available options can be demonstrated would fecal DNA testing be cost effective.

In 2004, Song et al. conducted an economic analysis of fecal DNA tests using Markov modelling. The analysis compared fecal DNA testing and FOBT and/or sigmoidoscopy versus colonoscopy. The study found that fecal DNA testing was cost-effective compared to no screening but was less cost-effective than conventional FOBT and colonoscopy.

Since these cost-effectiveness studies were published, fecal DNA tests have evolved and costs have come down. Indeed, each of these studies based their results on early versions of the fecal DNA test. Next-generation versions are intended to offer numerous improvements on older versions, including better sensitivity and lower costs. Still, further analysis is needed to address the cost-effectiveness of newer versions of the test.

New and emerging alternatives

Other screening tests that are being developed as alternatives to CRC screening techniques include blood tests, a rectal mucous test, urine tests, saliva tests, and capsule colonoscopy.

Regulatory status

Health Canada has not currently licensed any fecal DNA test.

Conclusion

The technical challenges that compromised first-, second-, and third-generation versions of the fecal DNA tests are being addressed. Refinements in recent laboratory methodologies, additional improvements of panel biomarkers that maximize sensitivity and specificity for both advanced adenomas and cancer, and cost modifications are emerging. If DNA fecal testing can improve compliance and reduce unnecessary diagnostic follow-up compared with FOBT’s, cost savings may be realized. In addition, the demonstration of mortality benefit in clinical trials, evidence to assess the sensitivity and specificity of fecal DNA tests, and verification of optimal screening intervals are necessary before fecal DNA testing can be used as a CRC detection tool in average-risk screening populations.
References


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