EDITORIAL

FIT to be tried

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Colorectal cancer (CRC) screening has come of age in Canada, with every province now having a screening program either implemented or well underway. These programs are based on the detection of fecal occult blood, with positive results triggering colonoscopy for definitive diagnosis. This approach is supported by high-level evidence demonstrating a mortality benefit for individuals screened in this manner (1-3).

Fecal occult blood testing (FOBT) uses indirect methods to test for the presence of hemoglobin, which can be affected by chemicals, such as vitamin C, or heme from other sources such as red meat. In contrast, fecal immunochemical tests (FIT) use an antibody to detect human globin directly (4). These assays may offer advantages of greater specificity and sensitivity, and improved adherence. Most FITs produce a visual colour change on a strip to indicate a positive result, but some are analyzed using automated systems in a laboratory to provide a quantitative result.

In the current issue of the *Canadian Journal of Gastroenterology*, Rabeneck et al (5) (pages 131-147) report on the findings of the FIT Guidelines Expert Panel, a group convened to evaluate the latest evidence on the use of FITs and to advise 'ColonCancerCheck,' the Ontario CRC screening program (5). The group was specifically interested in FIT performance characteristics, usability factors and specimen stability.

Following a comprehensive search of the published literature between 1996 and June 2010, two systematic reviews, three randomized controlled trials and four other studies were reviewed in detail. The panel prepared a review of the 13 different FITs currently approved for use in Canada and reviewed websites of pertinent provincial and national health care organizations for relevant evidence.

Three studies compared FIT performance with standard guaiac FOBT (gFOBT). CRC detection was the primary outcome, but some studies also assessed advanced adenoma (AA) detection. Overall, FIT had higher positivity rates (4.8% to 11.2%) than standard gFOBT (2.4% to 7.9%), with similar or slightly lower specificity for CRC detection (90.1% to 95.8% versus 92.4% to 98.1%), resulting in a higher rate of detection of CRC and AA (1.4% FIT versus 0.6% gFOBT). Sensitivity was assessed in only one study, but was significantly higher for FIT for both CRC detection (92.3% versus 30.8% [P<0.01]) and AA detection (33.9% versus 13.6% [P<0.05]). One study compared FIT with Hemoccult SENSA (Beckman Coulter, USA), a more sensitive gFOBT. In that study, FIT positivity was significantly lower than Hemoccult SENSA (3.2% versus 10.1% [P<0.01]), but with significantly higher specificity for CRC (96.9% versus 90.1% [P<0.01]) and AA detection (97.3% versus 90.6% [P<0.01]). The positive predictive value (PPV) for detection of both CRC (5.2% versus 1.5% [P<0.01]) and AA (19.1% versus 8.9% [P<0.01]) was superior for FIT compared with Hemoccult SENSA.

Studies that evaluated different cut-off levels to define a positive FIT demonstrated increased PPV and specificity at higher cut-off levels (>100 ng/mL) at the expense of a decrease in positivity rate and sensitivity.

All three studies that evaluated patient participation rates noted significant differences in favour of FIT, with rates ranging from 59.6% to 68%, compared with rates of 46.9% to 55% for FOBT.

The authors were interested in assessing the temperature stability of FITs that used a vial collection method. One study that examined this reported lower positivity rates in warmer months (OR 0.83 [95% CI 0.73 to 0.90] summer compared with winter) and a reduced chance of a positive test for every increase of 1°C average ambient air temperature in the five to 11 days preceding test analysis (OR 0.993 [95% CI 0.989 to 0.996]). A recent Dutch study (6) made the same observations. However, in that study, return times of up to 10 days did not affect FIT performance, suggesting good specimen stability with respect to time to processing (6).

The findings of this expert panel suggest that FIT is superior to gFOBT for CRC screening. It has higher sensitivity, PPV and CRC detection rates compared with standard gFOBT, and greater specificity and PPV compared with the most sensitive gFOBT, Hemoccult SENSA. An additional advantage of FIT is superior performance in detecting AAs, enabling not just early detection of CRC but also true prevention by identifying advanced lesions that can be managed endoscopically. Perhaps of greatest importance, FIT is more acceptable to patients than gFOBT, with participation rates approximately 10% greater than for other FOBTs. This is likely related to a simpler specimen collection process, no requirement for dietary restrictions and, for most FITs, collection of just one specimen. Indeed, in northern California (USA), a significant improvement in CRC screening participation has been associated with the use of FIT in a comprehensive program, with participation rates rising from 35% in 2004 to 75% in 2011 (4).

Most FIT manufacturers recommend using a cut-off level of 100 ng/mL to define a positive test. However, adjusting that level downward alters the performance characteristics toward greater sensitivity and test positivity at the expense of less specificity and a lower PPV. There are resource implications associated with more positive screening tests (ie, more colonoscopies generated), but ultimately, this leads to more CRC detection. A Dutch cost-effectiveness analysis concluded that 50 ng/mL was the preferred cut-off level in their screening program (7). It is not known whether that result would apply to screening programs operating within Canada.

In conclusion, the FIT Guidelines Expert Panel has completed a comprehensive review of FIT for CRC screening. Their findings are consistent with those of other societies and provide a solid evidentiary base to implement FIT for CRC screening in Canada. Attention should be devoted to the temperature stability of FIT kits, a very relevant issue for the extreme seasonal temperature variations in Ontario and other parts of Canada. Further investigation should be conducted to allow for the identification of the optimal cut-off point to define a positive test.

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