The Ontario Colon Cancer Check (CCC) Screening Program

By: Joel Goodman, PhD, FCACB
Gamma-Dynacare Medical Laboratories
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Cancer Care Ontario (CCO) in association with the Ontario Ministry of Health (MOH) launched an Ontario-wide colorectal cancer screening program on April 1, 2008. The Ontario ColonCancerCheck (CCC) program was first announced in January 2007. It was to be the first province-wide, population-based colorectal cancer screening program in Canada, although similar programs in most other Canadian provinces have since been announced (data from the Canadian Partnership Against Cancer, April, 2009) and are now either in the pilot, phased implementation or planning implementation stages.

The Ontario "Colon Cancer Check" (CCC) program is family physician directed and geared to Ontario residents at low/average risk for colorectal cancer. Patients are advised to visit their family physicians to be educated about why and how to participate in the CCC program, and to obtain their fecal occult blood test (FOBT) kit. Patients who do not have family physicians can receive their consultation and FOBT kits from any Ontario pharmacist or by placing a call to TeleHealth Ontario. All patients with positive FOBTs (even a single positive "window" is considered a positive result in this program) are referred for colonoscopy. Those judged to be at high-risk for colorectal cancer are not offered the FOBT and are instead referred directly to colonoscopy. More details of the Ontario CCC program are available at http://coloncancercheck.ca/.

The screening test selected for the Ontario Colon Cancer Check (CCC) program was the guaiac-based FOBT (g-FOBT). In other countries where colorectal cancer screening programs operate, most have opted for the g-FOBT although some Canadian provinces (British Columbia, Saskatchewan, and Nova Scotia) have selected an immunological FOBT (i-FOBT). The selection criteria for the FOBT to be used in the screening programs are not generally elaborated upon in the literature; however, it seems safe to conclude that decisions have been made based on a combination of quality (sensitivity and specificity) and cost. In Ontario, the CCC program was mandated to use a g-FOBT; however, an i-FOBT may be considered in the future.

The relatively large number of tests (500,000 per year) that needed to be performed for this program in Ontario (population about 12 million) necessitated their allocation to laboratories capable of high-volume testing. The MOH additionally decided that all licensed and accredited commercial medical laboratories in Ontario were entitled to participate in the program.

A committee to determine the laboratory standards for the g-FOBT was convened under the direction of Dr. Linda Rabenek of CCO. The findings and recommendations of this committee were published (Rabenek et al; Clin Biochem 2008; 41: 1289-1305) and set the standards for patient preparation and specimen collection, as well as for all testing and reporting protocols. Another of the mandates of the program as outlined in the Rabenek article was participation in an external quality assurance program, a standard

deemed necessary from results obtained in an earlier MOH/CCO-sponsored FOBT pilot study in Ontario.

The pilot study had revealed inter-laboratory discrepancies in several parameters of testing quality, the most significant of which was the FOBT positivity rate. In the Ontario CCC program, all patients with positive FOBT results are referred for colonoscopy. False positive FOBTs therefore unnecessarily send patients to colonoscopy (with its inherent risks), while false-negatives miss potential cancers and defeat the entire purpose of the screening program. As such, the ramifications of FOBT reading errors are significant.

At the onset of the CCC program, Ontario (QMP-LS) did not have an external quality assurance (EQA) program for FOBT. While this seems surprising given that the FOBT is a cancer marker and that its result directs treatment, the lack of such a program may have been due to appropriate quality control material not being readily available. When the CCC program was conceived, several Ontario medical laboratories (both hospital and commercial) had been utilizing saline solutions of hemoglobin at appropriate concentrations to control their occult blood assays. Those laboratories participating in the College of American Pathologists' (CAP) EQA program did receive test samples with stool-like matrix; however, the hemoglobin concentrations in these samples produced only strong positive or negative results. Challenge specimens with hemoglobin concentrations at the FOBT card cut-off were not available from CAP. In addition, laboratory validations of g-FOBT card sensitivities using a material with appropriate matrix, as well as estimates of lot-to-lot variation in both card and developer performance, were largely unavailable.

Based on the criteria specified in the g-FOBT Laboratory Standards guideline (Rabenek et al, 2008), a supplier of g-FOBT kits was selected. The vendor was mandated to provide technologist training programs on an "as required" basis. The training programs provided specimens for analysis as well as photographs of FOBT cards containing stool specimens with varying amounts of hemoglobin that had been developed and photographed within their prescribed time intervals.

To fulfill the Ontario Ministry of Health's mandate for an EQA program in which all laboratories providing testing for the CCC program were required to participate, an FOBT Quality of Care (QofC) Committee was formed. The membership of the committee was drawn in an equitable fashion from the professionals working in the commercial laboratories, with one seat for a representative of the Ontario Association of Medical laboratories (OAML). Manufacturers of quality control materials were contacted and asked if they had or could provide a stable, stool-like matrix containing specified amounts of purified human hemoglobin. Dr. David Seccombe and the Canadian External Quality Assessment Laboratory Inc. (CEQAL) provided the best solution and agreed to work closely with the newly formed Qof C Committee.

CEQAL performed a series of studies using both the routine g-FOBT cards as well as with the CCC program-specific g-FOBT cards. A suitable matrix was created and was

subsequently spiked with varying concentrations of purified human hemoglobin. It was determined that this matrix would be used for the EQA program and similar material would also be made available to laboratories for use in daily internal quality control programs. Sensitivity of each lot of FOBT cards, stability of the matrix, effect of temperature and freezing on the matrix, and the lot-to-lot variability of both the card and the developer were determined by CEQAL and reported to the QofC Committee. As a result of these studies, protocols for storage and use of internal quality control material were developed and mandated for all participating laboratories.

The CEQAL studies revealed discrepancies between the manufacturer's stated specifications for their g-FOBT cards and the actual performance of these cards with the CEQAL hemoglobin-spiked synthetic matrix. The lot-to-lot variation within the Cards appeared to be significant, varying between 0.7 – 1.4 mg of hemoglobin per gram of synthetic matrix.

On another front and before the CCC program began, laboratories began looking into the performance of their own g-FOBT kits. A significant location-to-location variability was discovered by several laboratories even though the same manufacturer and lot number of card were employed. This was found despite colour-blindness testing, regular competency assessments for technologists reading the cards, routine use of a saline-based quality control material and participation (with perfect performance) in the CAP FOBT EQA challenges. The most significant factor in achieving consistent results with g-FOBT testing appeared to be technologist training, since the technologist "trainers" in each location were never "retrained" together with their peers or to some gold-standard
e.g. an immunochemical FOBT test, a hemoglobin-spiked, stool-like matrix sample or even by the kit manufacturer to their specifications.

The QofC Committee worked with an independent vendor (DigitalPT/HealthMetrx) to manage the FOBT QofC EQA program. The QofC Committee also mandated that all laboratories planning to participate in the CCC FOBT screening program must (a) participate in a manufacturer's training seminar before they begin testing, (b) join the FOBT QofC EQA program and pass at least one QofC EQA challenge prior to testing for the CCC program and (c) participate in a technologist-exchange program (one or more technologists from one laboratory visit another participating laboratory and sit at their bench and read developed FOBT cards alongside the bench technologist and compare results afterwards) prior to or soon after their CCC program FOBT testing had started. In the EQA program, three challenge EQA samples on a single card, each with an unknown amount of hemoglobin (0 – 2.5 mg Hb/g matrix), are distributed monthly to each participating laboratory. A policy for how the QofC Committee deals with EQA errors was developed and distributed to each participating laboratory.

A series of best practice protocols were developed by the QofC Committee so that the entire FOBT testing process could be standardized. Thereafter, in addition to monitoring FOBT quality with the EQA program on a monthly basis, a series of "Key Performance Indicators" or KPI data are required to be submitted monthly by each testing laboratory. These data must include the laboratory's performance on their internal quality control

samples, positivity rates for patient samples, and rejection rates (including a report on the causes for rejection of either the entire FOBT card or for one or more of the flaps on the card, as per the protocols for specimen rejection developed for the program).

The testing began in April, 2008, with four laboratories (accounting for about 95% of all CCC FOBT testing in this program) participating. As had been seen previously in the CCO FOBT pilot project, significant differences in rejection rates and positivity rates between participating laboratories were seen initially. The QofC Committee's mandate and operating protocols were instrumental in improving performance in all areas of the FOBT testing by all laboratories. As new laboratories joined the CCC testing program, the established guidelines quickly brought these laboratories into line with their peer group.

The technologist-exchange program, implementation of standardized daily internal quality control programs, results of EQA challenges, and the comparison of all-patient data with the peer group, have all contributed to data standardization and to more accurate and reliable FOBT data. Colonoscopy results are not yet available to the QofC Committee. However, once they become available, the predictive value for positive FOBTs in this program will be determined on a lab by lab basis. This will provide further feedback as to the quality of the FOBT testing being performed for this program. The result of this emphasis on quality will be improvement in the predictive value of the screening and therefore a benefit to all of the patients in the program.

In conclusion, much has been learned about the g-FOBT from the introduction of the Ontario CCC screening program. A test that previously appeared to be given little attention as far as quality was concerned has evolved into a well controlled assay in Ontario's commercial clinical laboratories. The EQA program is now available to all of Ontario's hospital laboratories as well as laboratories in other provinces. However, it remains to be seen if others choose to utilize now-available quality control material and embrace the challenge of assessing the quality of their g-FOBT, or instead choose to simply render the g-FOBT test obsolete and employ more costly alternative tests (e.g. i-FOBT; DNA markers etc.) for colorectal cancer screening.