
INTRODUCTION

The goals of The World Endoscopy Organisation (WEO) Colorectal Cancer Screening Committee (CRCSC) are:

• To provide a forum for international professional interaction in the area of screening for colorectal cancer (CRC).
• To promote innovation (developing, testing and promoting advances) and effective practice in the screening and surveillance for CRC.
• To collaborate with fellow professional associations seeking to promote prevention of CRC.

Each year, the CRCSC holds several workshops around the world, amongst a range of activities, that consider topical issues of relevance to our goals.

We report on our workshop held in May 2011, in Chicago adjacent to DDW, which addressed the following themes:

1. How are the newer markers shaping up as replacement for fecal occult blood tests (FOBT)?
2. Progressing implementation from laboratory discovery to population application
3. Review of the international Endoscopy Trials

We can expect to see significant changes in how we screen for colorectal cancer over the next decade. Molecular tests, based on fecal or blood samples, are promising in terms of clinical performance and acceptance. The optimal strategy for offering screening remains to be defined. Offering choice of test need not confuse the invitee, provided that this is structured in a sequential manner. It is difficult to compare results between studies using different FIT (fecal immunochemical tests for haemoglobin) products; introduction of a standard method for reporting fecal hemoglobin concentrations would solve this. A number of trials of screening colonoscopy are now underway. These will provide clear guidance about the acceptance, feasibility and value of this invasive screening tool relative to simpler screening tests. Comparative Effectiveness Research, will enable us to objectively compare two or more interventions in a head-to-head design where a major service program is already implemented.
New Developments in Screening for Colorectal Cancer

**PRACTICAL APPROACHES TO THE DIAGNOSIS AND TREATMENT OF COLORECTAL CANCER #9**

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Copies of author-approved presentations are available at the following website: http://www.worldendo.org/presentations-crc-2011.html

**Session 1:
How are the Newer Markers Shaping Up?**

**New Molecular Markers**

More specific markers for neoplasia are of great interest as FOBT are not directed at neoplasia-specific events. Detailed updates were provided on three molecular markers – Cox-2, M2-PK and Septin-9.

Prof Shigeru Kanaoka (Hamamatsu University, Japan) provided an analysis of the status of fecal cyclooxygenase 2 and matrix metalloproteinase 7 mRNA expression using quantitative real-time RT-PCR and their usefulness in lesion detection. It was reported that COX-2 and MMP-7 mRNAs in feces were not upregulated in subjects with small adenomas, upper GI cancer, or healthy controls. In contrast, fecal RNA testing targeting COX-2 and MMP-7 mRNAs expression did show promise for detecting CRC and advanced adenoma. Comparing 145 subjects with neoplasia to 113 normals, they showed that the specificity of combination of COX-2 and MMP-7 was 99.1%, while that of a FIT (fecal immunochemical test) was 98.2%. The sensitivity of each assay for CRC was 75.7% for COX-2, 55.9% for MMP-7, respectively, while that of FIT was 66.7%.

Prof Sybille Mazurek (University of Giessen and ScheBo Biotech AG Giessen Germany) updated the status of the M2-PK marker in feces. The dimeric form of M2-PK is released as a metabolic biomarker due to changes in glucose metabolism. A literature search identified twelve independent published studies incorporating a total of 704 stool samples from CRC patients with a mean fecal M2-PK sensitivity for CRC of 80%. Three independent studies conducted a head to head comparison against gFOBT (guaiac FOBT) – a mean of 47% of adenoma >1 cm tested positive with fecal M2-PK, whereas gFOBT detected only 27%. In a study with head to head comparison of fecal M2-PK with four different FITs, M2-PK achieved a better sensitivity. From two studies totalling over 7,000 people, the authors estimated a specificity of 93.4% to 97.4% depending on the prevalence of neoplasia.

Prof Thomas Rösch (University Hospital Hamburg, Germany) provided an extensive overview on the application of the Septin-9 methylated DNA marker in blood. DNA is shed from colorectal tumors into the bloodstream and can be detected in the blood plasma using sensitive PCR. He reported that in the Presept study to date, 53 cancers have been detected with 64% sensitivity and 88% specificity, although it should be noted that further refinements of the method promise to improve this, especially sensitivity. This marker also performed well in proximal cancers.

**Detecting Right-Sided in Interval Cancers**

Two presentations then focused on whether or not these newer markers might assist with the challenge of detecting right-sided and interval cancers.

Prof Robert Steele from University of Dundee Scotland presented the characteristics of interval cancers (cancers diagnosed within two years of a negative gFOBT) in the Scottish program. Over three rounds of screening, many interval cancers were observed. In the first round 31.2% of the cancers diagnosed in the screened population were interval cancers. This rose to 47.7% in the second round and 58.9% in the third round. They showed that interval cancers are associated with a better prognosis than cancers arising in a non-screened population. In addition, gFOBT appears to preferentially detect cancers in males and the left side of the colon at the expense of cancers in females and in the right colon and rectum.

This was followed by a presentation from Dr. Steven Itzkowitz describing the value of fecal molecular tests in the detection of proximal cancers. He pointed to the technological improvements that have resulted in better DNA preservation during specimen transport, enhanced DNA extraction from stool, and perhaps most importantly, the recognition that hypermethylation of particular genes can be highly sensitive and specific markers of CRC, adenomas, and serrated polyps. Of the newer studies, when colonic location has been considered, almost all studies have shown that methylation markers recognize proximal colon cancers (and even adenomas) at least as well as distal lesions. This is not the case for gFOBT and FIT.

**Standardising the Reporting of FIT**

The point that FIT, a new technology now replacing gFOBT, are actually molecular tests is often overlooked. Antibody specifically directed against human haemoglobin is used and these tests are therefore “molecular” in nature that they target a specific
molecule. Of great concern to researchers in the field has been the fact that the standards of quality assurance and reporting that are usually applied to laboratory tests have not been applied to FIT.

Professor CG Fraser (University of Dundee, Scotland) discussed the problems of comparability across different FIT products. He reported that different FIT products have different clinical performance characteristics but comparison was difficult because manufacturers used different approaches to determine and express the cut-off hemoglobin concentration used to define positivity. For instance, some report amount of hemoglobin in test buffer while others reported amount of hemoglobin in feces. He advocated that units of µg Hb/g feces be used ubiquitously and that manufacturers follow international guidelines. These provide guidance for performing uniform well-defined studies that can be used to adequately evaluate and describe performance characteristics of qualitative tests. Quantitative FIT are now being increasingly used and investigators are choosing a cut off concentration that suits their own population requirements. This compounds the problem of comparing results between studies using different products and he advocated that all manufacturers use µg Hb/g feces units, the mass of feces picked up in any particular collection device be documented, and the volume of buffer – if tubes are used as collection devices – also be documented. He closed by showing the well-developed hierarchy of methods and materials currently available to ensure comparability of serum cholesterol data over time, geography and method and recommended that FIT be subject to the same standards.

**Choice of Screening Test**

The first was the issue of providing choice of screening test, as guidelines generally allow. Prof Carlo Senore (CPO Piemonte, Turin, Italy) discussed the pros and cons of screening with FIT versus flexible sigmoidoscopy (FS). While guidelines provide a range of screening test options and some indicate it is important to offer people a choice of screening test, available evidence indicates that uptake does not increase when people are offered a choice among proven-effective screening methods. In a large study of 43,748 in Turin and 19,970 in Verona, they found that a strategy involving sequential offer of first FS and then FIT to non-FS-participants represents an efficient approach to allow for the implementation of subject’s preferences without undermining equity of access or creating confusion by offering a choice. FIT in people not attending for FS resulted in a substantial increase in screening uptake and contributed to detection of additional advanced adenomas and CRCs.

**Blood or Feces as the Sample to be Tested**

With the appearance of blood-based screening tests, such as Septin-9, it is important is to understand how an invitee to screening would view provision of a blood test compared to a fecal test. Ms Joanne Lane (Flinders University, Australia) presented the results of a recent qualitative study addressing people’s attitudes to blood compared to fecal sampling. This study found that people overwhelmingly preferred a blood sample over a stool sample for a CRC screening test. Preference was influenced by gender, experience with sampling method and the individual’s perception of sampling convenience, sampling comfort and sample acceptability.

**Participation Over Multiple Rounds of Screening**

The final of the three issues discussed concerning the encouragement of participation, was the challenge of how best we should describe participation over multiple rounds of screening. Prof Graeme Young (Flinders University, Australia) pointed out that there was no generally agreed, practically-useful systems for describing participation over multiple rounds. This has been inadequately addressed in the literature, has been incompletely reported in a constructive fashion in studies where multiple rounds had been undertaken, and the behavioural associations with certain patterns.
of participation have not been clearly described. It was proposed that rather than simply describing people according to the number of times they participated — for instance, as nonparticipants in all rounds, participants in all rounds, or participants in a given proportion of rounds, we should describe participation according to whether or not changes in participation had occurred and whether or not these had been sustained. This would give more information about the individual and the choices they make. Ideally using a system such as this would enable us to identify behavioural characteristics around which we could then derive new intervention strategies designed to improve ongoing participation.

How Many Fecal Samples do We Need?

One of the crucial issues for application of FIT in population screening is the number of samples, the frequency of testing and the hemoglobin cut-off concentration to use. It should be noted that the capacity to choose a cut-off (using a quantitative FIT) enables one to adjust the positivity rate according to resource availability (number of colonoscopies) and feasibility, not just clinical outcomes. Prof Ernst Kuipers from the Netherlands (Erasmus University Medical Centre) presented an extensive summary of the data from the Netherlands population studies (over 15,000 individuals naïve to screening) to give guidance as to the trade-offs and advantages of using different numbers of samples and the different cut-offs. His presentation gave clear guidance as to what these would be. The major conclusions reached were:

1. FIT screening outperforms gFOBT in terms of adherence (participation) and yield of neoplasia
2. Low hemoglobin cut-off FIT screening is most efficient across every interval and age range assessed
3. The choice for 1- or 2-sample FIT screening depends on resources. The optimal return on investment is achieved when colonoscopy is triggered by the following scenarios:
   • very limited resources: use 2-sample screening and colonoscope only if both are positive
   • unrestricted resources: use 2-sample screening and colonoscope if either is positive
   • intermediate situations: use 1-sample screening and choose a cut-off to reflect resource availability
4. Variation in FIT screening interval between 1 and 3 years does not affect participation rates.

Undertaking Research When National Programs are in Place

The final presentation in the session came from Michael Bretthauer from Norway (Oslo University Hospital) who addressed the issue of how we might conduct screening research in environments where major population screening programs have been implemented within the structure of health care systems, and where the capacity to test innovative ideas, new technology and new behavioural strategies might be compromised because of the scope and often rigid nature of the program and its implementation. He proposed that we use Comparative Effectiveness Research (CER), defined as “the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition, or to improve the delivery of care”. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels.” (http://www.nap.edu/catalog.php?record_id = 12648). This enables us to objectively compare two or more interventions in a head-to-head design where a major service program is already implemented. He explained how this has been implemented in Norway without compromise to the program.

Session 3: International Endoscopy Trials

While there is substantial randomised controlled trial evidence to support screening based on FOBT or FS, the evidence for the value of colonoscopic screening is less direct and remains subject to bias. In recent years there has been strong support for the establishment of randomised controlled trials of the value of colonoscopic screening. There are many reasons for this, but uncertainties remain about the incremental benefit of colonoscopic screening and especially as to whether that benefit is worth the extra effort required to implement it on a broad and equitable basis within a community. There are also major concerns about the acceptability of such screening. Consequently, a series of presentations (continued on page 34)
addressing the status of colonoscopic and FS screening trials and efforts to introduce colonoscopic screening within healthcare programs was provided.

The issue of appropriate follow-up algorithms for patients found to have adenomas in a screening program is crucial to the colonoscopic burden created by screening programs. Understanding whether these algorithms should be the same across the world or different according to the circumstances that apply within an individual country, is an uncertainty for screening programme implementers. Professor Takahisa Matsuda (National Cancer Center Hospital, Japan) updated progress on the study that commenced in 2003, where they have randomised 3,926 patients to follow up after diagnosis of a colorectal adenoma and achievement of a clean colon. He reported interim results on quality and intermediate outcomes and indicated that results will be available by mid 2012. This will enable comparison of results with previous findings in countries such as the Americas and Europe.

Updates were provided on eight endoscopic screening studies or programs under way.

**Italian SCORE Study**
A single sigmoidoscopy (FS) at around age 60 has been proposed as a cost-effective strategy to prevent CRC. Prof N Segnan (CPO Piemonte, Italy) reported on the conduct of a randomised controlled trial in 6 centres in Italy designed to estimate the impact of this strategy on CRC incidence and mortality and the duration of the protective effect. FS screening offered once in a lifetime was observed to be associated with a substantial reduction of CRC risk at a relatively early time point (interim analysis). Longer follow-up is needed to accurately estimate the effect on CRC mortality.

**The PLCO (Prostate, Lung, Colorectal, and Ovarian) Trial**
This is a multicenter randomized cancer screening trial that includes FS. Dr Robert Schoen (University of Pittsburgh) reported that enrolment in the trial began in November 1993 and continued until July 2001. Nearly 155,000 subjects were enrolled. Final conclusions from the PLCO trial await comparison of CRC mortality and incidence in the intervention versus the usual care arm.

**NORDIC and NORCCAP Studies**
Dr. Michael Bretthauer reported on their status. For the NORCCAP study, 55,736 individuals (age 55-64 years) from Norway were randomised from the population registry to once-only FS with or without a single round of FOBT (n=13,823), or no screening (n=41,913). After 7 years follow-up, by intention-to-screen analysis there was a trend towards reduced CRC mortality (HR=0.73, 95% CI 0.47 to 1.13, p=0.16). For attendees compared to controls, a statistically significant mortality reduction was observed for total CRC (HR=0.41, 95% CI 0.21 to 0.82, p=0.011) and rectosigmoidal cancer (HR=0.24, 95% CI 0.08 to 0.76, p=0.016). The next analysis is planned after 10 years of follow-up.

The Nordic-European Initiative on Colorectal Cancer (NordICC) is a multinational, randomized trial investigating the effect of colonoscopy screening on CRC incidence and mortality. For 80% power and a two-sided alpha level of 0.05, 44,000 individuals will be randomised to control, and 22,000 individuals to the colonoscopy group. The NordICC trial has been recruiting individuals since July 2009, at centres in Poland, the Netherlands and Norway. So far, more than 5,500 individuals have been screened. Screening will start in Sweden in late 2011. Recruitment is planned to be finished by the end of 2012.

**COLONPREV Study**
Colorectal Cancer Screening in Average-Risk Population: a Multicenter, Randomized Controlled Trial Comparing Immunochemical Fecal Occult Blood Testing versus Colonoscopy (COLONPREV) is being carried out in 8 Spanish regions (Aragón, Canarias, Catalunya, Euskadi, Galicia, Madrid, Murcia and Valencia). Prof Antoni Castells (Spain) reported that eligible subjects were stratified by age and address, and randomized (1:1) into two study arms: group I, biennial FIT followed by colonoscopy when a positive result; group II, colonoscopy. The study started in November 2008 and a first preliminary analysis is planned for July 2011.

**UK Flexi-Sig Study**
FS screening, offered on a single occasion to men and women aged 55-64 years, has been tested in two large trials in the UK and Italy for capacity to to provide a substantial and long-lasting reduction in CRC incidence and mortality. Prof Wendy Atkin (Imperial College London) reported that in response to this evidence, it is planned to extend the existing English Bowel Cancer (continued on page 36)
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Screening Programme (BCSP), which offers gFOBT to men and women aged between 60 and 74 years, to include a single FS screen at age 55. The FS programme will use the infrastructure of the BCSP. The five regional Hubs, which are responsible for invitations and analysis of FOBT tests, will invite the population for FS screening and send out enemas for self-administration. The nationwide initiative to increase the quality and safety of colonoscopy in all endoscopy units, with accreditation for endoscopists participating in the BCSP, will be extended to include unit and endoscopists performing flexible sigmoidoscopy. Repeated surveys of all English endoscopy units using the Global Rating Scale (http://www.globalratingscale.com/) confirm that quality has improved consistently. Application of this survey to FS will be important in ensuring the safety of the extended programme.

CONFIRM Trial
Colonoscopy vs. Fecal Immunochemical Test in Reducing Mortality from Colorectal Cancer (CONFIRM). The CONFIRM trial is a large, simple, multicenter, randomized, parallel group trial directly comparing screening colonoscopy with annual FIT screening in average risk individuals. Professor Douglas Robertson (VA Medical Center Vermont USA) reported that they will recruit 50,000 participants to test the primary hypothesis. The primary study endpoint will be CRC mortality within 10 years of enrolment. The planned study duration is 12.5 years with 2.5 years of recruitment and 10 years of follow-up for all enrolled participants.

German National Program
Prof Wolff Schmiegel (Bochum, Germany) reported that in autumn 2002 colonoscopy was introduced as part of a nationwide opportunistic screening program in Germany and offered to the general population 55 years of age or older. The findings of the first six years of the screening program were prospectively collected and analyzed. 2,821,392 colonoscopies performed between January 2003 and December 2008 were available for analysis. The cumulative participation rate was 17.2% of eligible women and 15.5% of eligible men between ages 55 and 74. Adenomas were found in 19.4% with a higher detection rate in men (25.8%) than in women (16.7%). Advanced adenomas were found in 6.4% of patients. Carcinomas were detected in 25,893 subjects (0.9%), the majority in an early tumour stage (UICC I 47.3%, UICC II 22.3%, UICC III 20.7%, UICC IV 9.6%). The overall complication rate was 2.8/1,000 colonoscopies, the rate of serious complications was 0.58/1,000 colonoscopies.

COMMENTS
Judging on the reports of these important and innovative studies, we can expect to see significant changes in how we screen for CRC over the next decade. Molecular tests are promising in terms of the clinical performance and their potential acceptance by the general screening population. They have the potential to overcome some of the shortcomings of FOBT but whether they will replace FOBT or be used in a complimentary fashion is unclear. The optimal strategies for offering screening remains to be defined. Offering choice of test need not confuse the invitee, provided that this is structured in a sequential manner. While FIT have become the FOBT technology of choice, it remains difficult to compare results between studies using different manufacturer’s products; it would be ideal if a standard method for reporting fecal haemoglobin concentrations were adopted by all manufacturers. In countries where CRC is a significant burden, national screening programs are being introduced but these should not compromise the conduct of large-scale research in the face of the service programs, as has been demonstrated in Norway. A significant number of screening trials of the value of screening colonoscopy are now underway. These will provide clear guidance about the acceptance, feasibility and value of this invasive screening tool relative to simpler screening tests.

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References