# Chicago 2014

## *5th Meeting of the Expert Working Group (EWG) – 'FIT for Screening'*

Friday, 2 May 2014: 08:30–11:30

## MEETING REPORT

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Expert Working Group (EWG) founding members:

- Jim Allison, University of California, San Francisco, USA (jallison@medsfgh.ucsf.edu)
- Callum Fraser, University of Dundee, Scotland (callum.fraser@nhs.net)
- Stephen Halloran, NHS Bowel Cancer Screening Programme & University of Surrey, UK (Chair) (s.halloran@nhs.net)
- Graeme Young, Flinders University, Australia (graeme.young@flinders.edu.au)

Summary report prepared by Helen Seaman (helenseaman@nhs.net).

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More than 70 delegates attended the EWG meeting in Chicago on 2 May 2014. Since the last meeting in Berlin (October 2013), the EWG has continued in its efforts to promote optimal use of FIT for colorectal cancer (CRC) screening.

## Session one: Stability – review of current evidence and strategies for minimising clinical impact

*Co-chairs: Professors Stephen Halloran & Graeme Young*

### 1.1. Introduction

*Stephen Halloran, NHS Bowel Cancer Screening Programme & University of Surrey*

The EWG publications, discussion documents and meeting reports are detailed on dedicated web pages: http://www.worldendo.org/weo-crcsc-expert-working-group-fit-for-screening.html.

EWG publications now include an evaluation of four quantitative FIT devices deemed suitable for population-based cancer screening completed by the Guildford Medical Device Evaluation Centre (GMEC) (November 2013). The four FIT systems evaluated were (a) HM-JACKarc, Kyowa Medex Co Ltd, Japan; (b) NS-Plus Hb, Alfresa Pharma Corp, Japan; (c) OC-SENSOR DIANA, Eiken Chemical Co. Ltd, Japan; (d) FOB Gold NG, Sentinel CH. SpA, Italy using the BioMajesty analyser, Sysmex UK. The full FIT evaluation report is also available online: http://www.worldendo.org/fit-ewg-publications.html

The important issue of FIT stability was highlighted in 2009 when the National Bowel Cancer Screening Programme (NBCSP) in Australia experienced the problem of reduced positivity in hot summer months. In 2010, investigators in Italy confirmed a seasonal variation in FIT positivity and noted a

reduction of about 13% in the number of cancers and advanced adenomas detected during the summer months [1]. Seasonal variation in FIT positivity in a cooler climate was also reported by Dutch investigators [2].

### 1.2. Experience with MagStream in Australia

*Graeme Young, Flinders Centre for Innovation in Cancer*

The NBCSP in Australia has used the MagStream HemTube FOBT (Fujirebio Inc., Japan) FIT system since 2006. In 2009, the NBCSP was suspended after a marked drop in positivity (from 6.6% to 3.5%). A new collection tube (New HemTube) had been introduced by the manufacturer in 2008 and reduced sample stability at high temperatures became evident quite quickly. The programme restarted in 2009 when New HemTube was replaced with New HemTube (B) and changes were made to guidance on handling and processing samples, *e.g.* kits not sent out when temperatures exceed 30.5°C (declaration of 'hot zones'), enhanced collection and storage advice to participants and reduction in the allowable return time from one month to 14 days. Positivity with the New HemTube (B) collection device (at June 2011) was 7.7%, higher than with the original HemTube, probably because of improved faecal haemoglobin stability and the measures put in place to avoid the exposure of samples to high temperatures.

Full details are available from the National Bowel Cancer Screening Program Monitoring Report, Phase 2, July 2008-June 2011 (The Australian Institute of Health and Welfare, 2012) (http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=10737421430)

### 1.3. Experience with OC-SENSOR in Australia: positivity and temperature effects

*Erin Symonds, Flinders Centre for Innovation in Cancer*

A pilot screening programme has been running for five years offering annual screening using two-sample OC-SENSOR. FIT kits are mailed out and returned to the laboratory by regular post. The cut-off for positivity (and referral to colonoscopy) is set to $\geq$ 20 µg Hb/g faeces ($\geq$ 100 ng Hb/mL buffer). The pilot programme has provided an opportunity to investigate the effect of temperature on FIT (OC-SENSOR) positivity, taking into account other factors that influence test outcome (age, sex, socioeconomic status, medical history, screening history, sample return time).

A laboratory study (using the 'old' buffer) analysed samples from the programme positive at a cut-off of $\geq$ 50 ng/mL stored and reanalysed 1-14 days later. Samples stored in a freezer showed an initial marked and sustained drop in Hb concentration and samples stored at room temperature also showed an initial drop in Hb concentration. There was little change in the Hb concentration of refrigerated samples.

More than 34,000 people have been offered screening in the pilot programme over the last five years – 64% completed kits, uptake is higher amongst women. Positivity is 6.2% and colonoscopy reports are available for 85%. Data from the pilot programme were analysed to identify factors associated with FIT positivity. Available information included 1,050 colonoscopy reports from subjects who had had a surveillance colonoscopy within a year after a negative FIT. Multivariate analysis confirmed higher positivity with increasing age, being male and a lower socioeconomic status. Reduced positivity was

associated with previous participation and high temperatures. Data on the storage conditions before return to the laboratory were available for one third of kits – most were refrigerated. There was no significant effect of storage or sample return time on positivity, after adjusting for other factors. The temperature on the day of sample return did, however, affect positivity – higher temperatures reduced the number of positive tests returned. For each one degree °C increase in the temperature recorded, positivity was decreased by 1.7%.

There was no change in the number of advanced adenomas and cancers detected through the seasons (probably because of a higher level of bleeding), although fewer less significant lesions (non-advanced adenomas) were detected in the summer months.

Stability investigations are needed for other FIT systems.

*Comment*: It was noted that, if the number of advanced adenomas/cancers was the same in the summer as at other times of the year but that fewer non-advanced adenomas were evident, it may be reasonable to suggest that screening programmes create less of a burden on colonoscopy in the summer.

### 1.4. Ontario FIT Pilot - Phase 1. Laboratory studies of stability over time and temperature

*Jill Tinmouth, Sunnybrook Research Institute, Toronto*

ColonCancerCheck is Ontario's organised province-wide screening programme offering gFOBt to individuals with an average risk of CRC. In 2012, Linda Rabeneck *et al* prepared an evidence review [3] that recommended that FIT should supersede gFOBt and that a pilot study be conducted in Ontario to guide implementation.

The pilot has been conducted in two phases – laboratory and field (see Open Session for a report on the field study). The Phase I laboratory work included a stability study using five FIT devices and gFOBt (hema-screen). The FIT kits selected (two quantitative and three qualitative) were those approved by Health Canada, deemed suitable for population use and identified as point-of-care devices:

1. NS-Plus (Alfresa, quantitative FIT);
2. OC-SENSOR (Eiken Chemical Co., quantitative FIT)
3. Hema-screen SPECIFIC (Immunostics, qualitative FIT)
4. FOB Advanced (Ulti med, qualitative FIT)
5. Hemoccult ICT (Beckman Coulter, qualitative FIT)
6. hema-screen (Immunostics, guaiac FOBT).

Three *in vitro* stability studies used Hb-spiked human faeces at concentrations appropriate for the analytical sensitivity of each particular kit.

- Controlled sample stability study - samples (3-8 different Hb concentrations) stored at between -20°C and -15°C (frozen), 2°C to 8°C (refrigerated), 20°C to 22°C (ambient) and 45°C (elevated) for up to 60 days and using five FIT systems and one gFOBt (as listed above). 12-18 samples per kit stored at each condition. Multivariate logistic regression modelling was used to predict the time (days) until the probability of remaining positive dropped below 50%, 70% and 80% (for

quantitative devices, the cut-off for positivity was as per manufacturers' recommendations). Results for the 70% threshold:

- Frozen: all stable at 60 days except OC-SENSOR (14 days)
- Refrigerated: all stable at 60 days except FOB Advanced (4.2 days) and Hemoccult ICT (9.6 days)
- Ambient temperature: hema-screen stable at 60 days
- Elevated temperature: all poor except hema-screen stable until 52.3 days

- Controlled freeze-thaw study – three FIT and three freeze-thaw cycles (could only use FIT that could be measured repeatedly). Hb recovery was measured and compared with baseline for quantitative kits (n=12) for each cycle (for FOB Advanced (qualitative device) the number of specimens remaining positive after each cycle was calculated [n=6]).
  - NS Plus, OC-SENSOR and Hema-screen SPECIFIC most stable
  - Analytic sensitivity: Hema-Screen SPECIFIC < quantitative kits.
  - FOB Advanced and Hemoccult ICT performed less well.
  - Guaiac, very stable but poor analytic sensitivity

**Temperature recording device (see slide set 1.1.)**

*Stephen Halloran, NHS Bowel Cancer Screening Programme & University of Surrey*

An investigation was carried out by Professor Halloran's team in Guildford. A small box containing a temperature logger was passed from Hub to Hub within the BCSP through the regular postal system during the warm summer months of 2013. The temperature logger recorded marked fluctuations in temperature, in line with temperature data available from the UK Meteorological Office, although it was evident that at times the box was exposed to temperatures that spiked above the temperature recorded by the Meteorological Office. Thus, meteorological data may not accurately reflect extremes of temperature exposure in the postal system.

It was noted that FIT stability will be influenced by characteristics of the faecal sample itself, as well as by environmental factors, for example bacterial content, so laboratory studies cannot entirely predict stability.

**Stability data from FIT manufacturers (see slide set 1.1.)**

*Stephen Halloran, NHS Bowel Cancer Screening Programme & University of Surrey*

Three manufacturers of quantitative FIT (Alfresa [NS-Plus, data provided for NS-Prime], Eiken [OC-SENSOR] and Sentinel [FOB-Gold]) provided up-to-date (April 2014) stability information:

- Alfresa reported stability for four concentrations of Hb-spiked pooled negative faeces using a cut-off for positivity of 20 µg Hb/g faeces:
  - Hb residual ratio was more than 90% in all the samples over 33 days when stored at -40°C and 7°C.
  - Hb residual ratios were 72% and 54% in mid- and high-positive samples, respectively, when stored at 25°C for 14 days.

  - Hb residual ratios were 78%, 55%, and 37% in low-, mid-, and high-positive samples, respectively, when stored at 37°C for 7 days.

- Eiken reported stability of Hb-spiked faeces at 25°C and 37°C for three concentrations (40 µg Hb/g faeces, 80 µg/g and 160 µg/g) using 2012 buffer.
  - 40 µg/g samples remained stable over 10 days at both temperatures.
  - At 25°C, the more highly concentrated samples reduced to about 75% after 10 days; at 37°C samples reduced to 30-40%.

- Sentinel reported stability data for the new buffer (BH): (new buffer markedly more stable at 32°C compared with the old buffer)
  - a significant reduction in decrease of Hb concentration particularly at moderate and high room temperature;
  - improved stability irrespective of storage temperature (4°C vs 21°C) and Hb concentrations;
  - long lasting stability (at least 10 days) in refrigerated samples (4°C)

It is encouraging that FIT manufacturers have updated their buffers. The FDA has not yet approved the new OC-SENSOR buffer – clearance is expected in 6-12 months.

### Repeat assays from FIT sample collection devices

*Stephen Halloran, NHS Bowel Cancer Screening Programme & University of Surrey*

Another potential limitation to laboratory stability studies was highlighted, using the OC-SENSOR sampling tube as an example. During analysis, the tube is squeezed so that the buffer (plus any analyte) passes into the uppermost section of the tube for sampling. After sampling, the buffer flows back into the bottom of the tube. The uppermost section of the tube is lined with filter paper and during storage the concentration of the analyte in the buffer solution dissolved on the filter paper will increase and affect re-assay. It is recommended that, if stability studies are conducted over time on the same sample, then the contents of the sampling tube should be decanted into another vessel (sampling cup) before storage and further analysis.

## Session two: Selection of cut-off faecal haemoglobin concentration(s) for use with FIT for screening

*Co-chairs: Professors Callum Fraser & Ernst Kuipers*

### 2.1. Factors that affect faecal haemoglobin concentration and implications

*Callum Fraser, Centre for Research into Cancer Prevention and Screening, University of Dundee*

The cut-off for qualitative FIT positivity is set by the manufacturer whereas the quantitative FIT faecal haemoglobin cut-off can be set by the user according to local requirements. The selection of a low cut-off for quantitative FIT increases positivity and the detection of disease, but lowers PPV and specificity [4].

Faecal haemoglobin concentration is directly related to the severity of disease but also varies according to sex, age, geography, level of deprivation and FIT analytical system used. The questions arise as to whether different cut-offs should be applied for different populations and/or should we individualise CRC screening by incorporating haemoglobin concentration and other known risk factors into a CRC risk-score?

It is evident that few countries are using quantitative FIT (most are using qualitative FIT).

***Countries using quantitative FIT – cut-offs used and rationale for choosing that cut-off:***

Scotland: the programme in Scotland is currently using a gFOBt as the initial screening test. A European tender has been issued by the Scottish Government following an evaluation study and cost-benefit analysis using OC-SENSOR. A high cut-off was used in the evaluation study (80 µg Hb/g faeces [400 ng Hb/mL buffer]) to limit positivity to about 2% (as for gFOBt) because colonoscopy resource is scarce.

England: a six-month FIT pilot started in April 2014 using OC-SENSOR (one in every 28 invitations is an invitation to complete a FIT rather than gFOBt). The cut-off has been set at $\geq$ 20 µg/g (100 ng/mL), which is expected to yield a positivity of about 6%. In the long-term, the cut-off will be adjusted according to colonoscopy resource.

The Netherlands: the Dutch programme commenced screening in January 2014 using Sentinel's FOB Gold with a cut-off of 88 ng/mL (15 µg/g and equivalent to OC-SENSOR 75 ng/mL). The cut-off is low and colonoscopy resource is scarce in the Netherlands, as elsewhere; it is anticipated that the cut-off may need to be increased. The referral rate is higher than anticipated from pilot studies, although initial invitations have been issued to older people within the target population (65 and 75- year-olds), which will affect positivity.

Spain – There are 17 autonomous regions in Spain – OC-Sensor is used in eight regions (with the same cut-off), two regions use FOB Gold (one or two samples) and four regions use another FIT. CRC Screening is now extended to the whole of Spain and FIT systems are chosen by region. The Basque Country is using OC-SENSOR with a cut-off of 100 ng/mL (20 µg/g) as recommended by the manufacturer and is experiencing pressure on colonoscopy resource.

Japan – there has been a national policy for CRC screening for men and women since 1992. Different prefectures using different FIT, although a two-day sampling method using OC-SENSOR is widely accepted. Various cut-offs are adopted by different prefectures – many are using 100 ng/mL (assuming OC-SENSOR, equivalent to 20 µg/g), others 150 ng/mL (30 µg/g) and a few use 200 (40 µg/g) or 300 ng/mL (60 µg/g).

Latvia – currently not using FIT for screening. A pilot study compared OC-SENSOR and FOB Gold at various cut-offs (50 ng/mL to 200 ng/mL). The cut-offs were translated to µg/g to assist comparison of the two devices. The number of advanced adenomas detected was similar with both tests – positivity was much higher with FOB Gold so more colonoscopies were performed to find the same number of lesions.

Czech Republic – problems have been reported with the programme. The choice of FIT device offered depends on the GP and a mixture of quantitative and qualitative devices is yielding a positivity >10%, which is stretching colonoscopy resource so much so that there are now questions as to whether the programme can continue.

The meeting was asked if manufacturers of quantitative FIT systems present actually do recommend a cut-off faecal haemoglobin concentration.

*Responses:*

Eiken Chemical Co. Ltd. – OC-SENSOR – no officially recommended cut-off.

Kyowa – HM-JACK series – recommend a cut-off as a starting point.

Sentinel – FOB Gold – the manufacturer does not suggest a cut-off. Cut-off should be determined by the experience of end-user and colonoscopy resource.

It is evident that countries using quantitative FIT adopt different strategies and that differences may exist even within a country.

As well as the presence of disease, FIT positivity depends on variables that include age, sex, socioeconomic status, country-specific factors and the analytical system used and reflects the number of people with a haemoglobin concentration above a predefined cut-off using a particular FIT device. This highlights the possibility that quantitative FIT provide an opportunity to set different cut-offs for different groups within a population and for different populations and the possibility of individualising medicine by developing a CRC risk score incorporating faecal haemoglobin concentration.

### 2.2. Risk scoring and faecal haemoglobin

*Ernst Kuipers, Erasmus MC, Rotterdam*

Quantitative FIT provide a faecal haemoglobin concentration, an opportunity to select and adjust the cut-off for test positivity and the possibility of developing individual screening.

Colleagues working in prostate cancer are far ahead of us. For example, the Prostate Cancer Risk Calculator (SWOP Prostate Cancer Research Foundation; http://www.prostatecancer-riskcalculator.com/) determines individual risk by selectively and cumulatively adding parameters, starting with age, family history and symptoms, and then incorporate the results of PSA testing, DRE *etc*. The tool can be used to validate new risk parameters and has a version for the screenee and for the physician as an open access web tool.

Individualised prostate cancer management – www.prias-project.org (Prostate cancer Research International: Active Surveillance) presents a programme in which men with early prostate cancer are managed according to close monitoring with early, curative treatment in those with evidence of biochemical or histological progression.

A recent study in the UK looked at incorporating non-genetic risk factors and behavioural modifications into risk prediction models for CRC [5]. A genetic analysis of the screenee to provide SNIP information

and a questionnaire to elicit information on alcohol intake, exercise, BMI, *etc.* allowed the investigators to quantify CRC risk and to identify individuals who should be targeted for screening first.

Other investigators from the Netherlands [6] reported that using a combination of the FIT result (positive/negative) with known CRC risk factors does better at finding people with advanced lesions than using FIT alone.

It would also be possible look at different FIT screening intervals over time or depending on presence of risk factors. Investigators found no advantage in terms of advanced neoplasia detection at the second round whether the screening interval was one, two or three years [7].

## Session three: Building interest in the use of FIT in the US

*Chair: Professor Jim Allison, University of California, San Francisco (UCSF)*

### 3.1. Introduction

*Jim Allison, University of California, San Francisco*

Since The NEJM published data on colonoscopy in 2000 [8, 9] and thought leaders in the US promoted screening colonoscopy as the "preferred and best" screening test [10], use of colonoscopy has increased, while use of any FOBT has declined.

Assertions about FOBT were made as follows:

- If FOBT/FIT are used, the opportunity for CRC prevention is limited and incidental.
- Screening for occult blood has been proven to be an inherently insensitive and non-specific marker for screen relevant neoplasia.
- Repeated testing is required and unlikely to be done.
- It is not the most effective screening strategy.

In 2012, change started, however, and there is now evidence that FIT is being recognised as a reasonable choice for CRC screening in average-risk populations:

- NCCRT/ACS FOBT Clinician's Reference Resource – 2012 (http://nccrt.org/about/provider-education/fobt-clinicians-reference-resources)
  - Screening for CRC: a guidance statement from the American College of Physicians [11]
  - Options for colorectal cancer screening. JAMA Patient Page [12]
- The New York Times 2013 - The $2.7 Trillion Medical Bill: Colonoscopies explain why U.S. leads the World in health expenditures (http://www.nytimes.com/2013/06/02/health/colonoscopies-explain-why-us-leads-the-world-in-health-expenditures.html?pagewanted=all&_r=0)
  - Screening and surveillance for CRC: state of the art [13]

### 3.2. FIT in the Kaiser Permanente System

*Jeff Lee, GI Fellow UCSF, Adjunct investigator Kaiser Division of Research*

Since 2007, Kaiser Permanente Northern California (KPNC) has sent FIT kits in the mail (out-reach) to average-risk individuals aged 50-75 years annually, offered FIT at Flu clinics (in-reach) and monitored colonoscopy follow-up. FIT used is one-sample OC-SENSOR (cut off 20 µg Hb/g faeces [100 ng/mL]) with automated analysis yielding dichotomous (qualitative) results. FIT and opportunistic colonoscopy for higher-risk individuals has resulted in screening rates reaching about 80% of the screen eligible population in 2013 (from about 50% in 2007), with concurrent increase in the proportion of CRC cases with localised disease.

FIT studies from KPNC:

- Allison JE, Tekawa IS, Ransom LJ, Adrain AL. A comparison of fecal occult-blood tests for colorectal-cancer screening. N Engl J Med 1996; 334(3):155-9. Epub 1996/01/18. [14]
- Allison JE, Sakoda LC, Levin TR, Tucker JP, Tekawa IS, Cuff T, et al. Screening for colorectal neoplasms with new fecal occult blood tests: update on performance characteristics. J Natl Cancer Inst 2007; 99(19):1462-70. Epub 2007/09/27. [15]
- Levin TR, et al. Adherence to annual fecal immunochemical testing in a large, community-based population. Gastroenterol 2013;144(Issue 5, Supplement 1):S-145. (Digestive Disease Week 2013). [16]
- Lee JK, Liles EG, Bent S, Levin TR, Corley DA. Accuracy of fecal immunochemical tests for colorectal cancer: systematic review and meta-analysis. Ann Int Med 2014; 160(3):171-81. [17]
- Mysliewic *et al*. Fecal immunochemical test performance over multiple rounds of annual testing in an outreach screening program. Gastroenterol 2014;146(5 (Supplement 1)):S-33. (Digestive Disease Week 2014 Chicago). [18]

### 3.3. FIT in the US VA System

*Jason Dominitz, Professor of Medicine, University of Washington School of Medicine*

Unlike in other screening settings, the faecal occult blood test was the dominant CRC screening test in the Department of Veterans Affairs (VA) system from the 1990s to 2003 [19]. Since then, colonoscopy has been gaining ground (now about 300,000 screening colonoscopies a year).

In 2013, there were about 900,000 FOBt performed (555,000 gFOBt and 345,000 FIT). Of the 555,000 gFOBt per year, 525,000 (95%) are part of a three-sample collection for screening (5.5% (individual) tests are positive); the other 5% (30,000 tests) are outside screening (*e.g.* POC, for GI bleeds) and 27.4% tests are positive. About 45% of the 345,000 FIT are one-sample (12.6% tests positive), 54% part of three-sample collection (9.6% positive) and the rest are POC/GI bleeds, *etc.* (28.5% positive). Overall FIT positivity in screening is 11%. The FIT used by VA system is OC-SENSOR (Polymedco) – the manufacturer requires processing of the FIT kits within 15 days of sample collection. FIT account for nearly 40% of all FOBt in VA system. In the VA system, a performance measure for gFOBt screening was that there had to be **three samples** and it has taken some time to revise the rules for FIT to only one sample being required. Some VA regions still use three samples for FIT.

There are lots of opportunities for research using VA data but little data analysis so far.

CONFIRM study (confirm: randomized trial of colonoscopy) has been designed to determine the true comparative effectiveness of colonoscopy relative to other proven non-invasive options (http://www.vaoutcomes.org/our_work/confirm/; http://clinicaltrials.gov/ct2/show/NCT01239082). The investigators have begun a large, simple, multi-centre, randomized, parallel group trial directly comparing screening colonoscopy with annual FIT (OC-SENSOR (Polymedco) cut-off ≥ 20 µg Hb/g faeces or 100 ng/mL) screening in 50,000 average risk individuals. The primary study endpoint will be CRC mortality within 10 years of enrolment. About 5,570 people randomised so far to FIT and 7.7% FIT positivity.

### 3.4. The 80% by 2018 campaign

*Richard Wender, Chief Cancer Control Officer, American Cancer Society, Inc.*

Ten drivers to the colon cancer screening opportunity now manifest as the '80% by 2018' campaign:

1. Several new reports confirm extraordinary progress [20].
2. The number of eligible adults with health insurance has grown.
3. Many financial barriers to screening are being eliminated.
4. FQHCs (Federally Qualified Health Centres) are now reporting colon cancer screening rates as one of the UDS (Uniform Data System) measures.
5. Emphasis on quality screening is accelerating.
6. The CRC screening efforts of the CDC funded 25 states and four Native American tribes are maturing.
7. The Patient Centered Medical Home (PCMH) has embraced cancer screening [21].
8. We have the tools and teams in place to catalyse a coordinated push – a collaboration of more than 80 organisations is working together as the National Colorectal Cancer Roundtable (NCRRT) to improve CRC screening rates.
9. An incredible group of organizations, leaders, and advocates is preparing to take a pledge. (Over 90 organizations, including gastroenterologists, anesthesiologists, pathologists, NACHC (National Association of Community Health Centers), AARP (American Association of Retired Persons), AAFP (American Academy of Family Physicians), state comprehensive cancer plans, hospital systems and others have signed a pledge to deliver coordinated, quality colorectal cancer screening and follow-up care to all people.)
10. The US Assistant Secretary of Health (Howard Koh) is expecting us to get this done.

Basic truths of colon cancer screening from the 2018 campaign:

1. If you only offer colonoscopy, you can achieve very good but not spectacular screening rates.
2. Even if you recommend colonoscopy for all, some people won't get one or can't get one. Using colonoscopy exclusively will, inevitably, lead to a screening gap.
3. Number of life-years gained is essentially identical regardless of screening strategy used (assuming 100% compliance) [22].
4. Faecal immunochemical tests (FIT) should replace guaiac FOBT.

5. Many patients prefer faecal tests [23-26].

How can Commission on Cancer (CoC)-accredited hospitals help the Nation achieve 80% CRC screening?

1. Sign the Pledge (www.nccrt.org).
2. Consider joining the NCCRT:
    a. Put the spotlight on colonoscopy co-pay issue
    b. Definition of screening colonoscopy
    c. Assessing Medicaid coverage of CRC screening.
3. Engage primary care networks.
4. Support policy solutions.
5. Develop smoothly functioning systems of care.
6. Monitor quality of screening.
7. Partner with FQHC's and other safety net care networks.
8. Monitor and report system-wide screening rates.
9. Make CRC screening a hospital and system-wide priority.

### 3.5. The CDC Program

*Djenaba Joseph, Medical Director, Colorectal Cancer Control Program, CDC*

The CDC's Colorectal Cancer Control Program (CRCCP) provides funding to 25 states and four tribes across the United States for five years. The CRCCP's goal is to increase CRC screening rates among men and women aged 50 years and older (both insured and uninsured) from about 64% to 80% in the funded states by 2014. The CRCCP uses colonoscopy and FOBT (http://www.cdc.gov/cancer/crccp/pdf/CRCCP_FactSheet.pdf).

### 3.6. Is there a role for a quantitative FIT in the US and, if so, how is the FDA a help or a hindrance to its availability?

#### Potential for quantitative FIT in the US

*Tom Imperiale, Professor of Medicine, Indiana University School of Medicine*

A study from investigators in Israel published seven years ago [27] reported the sensitivity and specificity of a quantitative FIT (OC-MICRO [Eiken Chemical Co. Ltd.]) for the detection of cancer and advanced adenoma in 1,000 patients undergoing colonoscopy and demonstrates how good FIT can be. The investigators sought to determine faecal Hb thresholds that give the highest post-test probability for neoplasia, and to determine the number of FIT needed. Some of the patients were asymptomatic but at increased risk for colorectal neoplasia and some were symptomatic. The haemoglobin content of three faecal samples was measured, and the highest value was compared with colonoscopy findings. Ninety-one individuals had clinically significant neoplasia – 17 cancers and 74 advanced adenomas. Sixteen of the 17 cancers were Dukes' stage A or B. The faecal Hb concentration was directly related to colonoscopy findings: normal colon mean faecal Hb 35 ng/mL [7 µg/g]; non-advanced adenomas 79

ng/mL (16 µg/g); advanced adenomas 485 ng/mL (97 µg/g); cancers 1,087 ng/mL (217 µg/g). The 95% confidence intervals around the mean faecal Hb measurements did not overlap in the progression from non-advanced adenomas, to advanced adenomas to cancer. The FIT sensitivity at $\geq$ 50 ng/mL (10 µg/g) was 100% for CRC and 73% for all clinically significant neoplasia (CSN); specificity was 84% and 89% respectively. At a cut-off of 100 ng/mL [20 µg/g] FIT sensitivity for CRC was 88% (specificity 90%) and sensitivity for CSN was 62% (specificity 93%).

Advantages of quantitative FIT from (a) the societal/health systems perspective – adjustable cut-off to manage colonoscopy resource and for triage and (b) the patient perspective – would providing a number (faecal Hb concentration) enhance adherence, possibility to increase cut-off for the elderly, tailor interval for re-testing according to faecal Hb concentration and potential to contribute to CRC risk score.

### Will the FDA help or hinder the adoption of quantitative FIT in the US

*Helen Landicho, Vice President Regulatory Affairs, Polymedco, Inc.*

Adoption of a quantitative FIT in the US would mean a change in the FDA-documented intended use of FIT, a requirement to demonstrate that the quantitative faecal haemoglobin concentration could be associated with disease state, the potential for FIT to triage and a change in the FDA's current perspective that colonoscopy is the gold standard and 'good' for 10 years.

The FDA bases approvals on the evidence – what does a 'positive' or 'negative' result mean in a normal risk US population and what is the role of FIT in GI pathology? Can FIT rule out bleeding from haemorrhoids? The FDA requires outcomes studies with definitive conclusions supporting the safe and effective use of quantitative FIT in the US, with risk stratification, health economics modelling and longitudinal data.

### 3.7. FIT in the uninsured/underserved US population

*Samir Gupta, Associate Professor of Clinical Medicine, University of California San Diego*

In the US, between 59-65% of the population is 'up-to-date' with CRC screening, but there are considerable disparities by race, ethnicity, education, income and insurance status [28, 29]. Some uninsured/underserved individuals are now acquiring health insurance through health reform and FIT promotion programs and research are confirming that FIT offers an opportunity to provide accessible and affordable CRC screening and to reduce the burden on colonoscopy resource [29, 30], although substantial infrastructure developments are needed to support the implementation of FIT in the US.

## Open session

### 4.1. Ontario FIT Pilot - Phase 2. A field study looking at methods of delivery and return

*Jill Tinmouth, Sunnybrook Research Institute, Toronto*

A field study ahead of implementation of FIT in Ontario to determine the impact on participation of two methods of FIT distribution (mail, pick-up) and two methods of FIT return (mail, drop-off). Four

combinations were tested in a cluster RCT design: (a) mail out/mail back, (b) pick-up/mail back, (c) mail out/drop off and (d) pick-up/drop-off. The FIT devices used were OC-SENSOR or NS-Plus (cut-off 15 µg Hb/g*) and outcomes assessed were FIT kit return within 6 months and positivity.

- Mail-out of FIT is superior.
- Two mailed contacts may be better than one.
- Drop-off of FIT similar to mail-back.
- Positivity declined with time and mail back.

**Note that collection devices are not exactly the same. OC-SENSOR stick collects 10 mg faeces into 2 mL buffer (conversion factor 0.2); NS-Plus stick collects 10 mg faeces into 1.9 mL buffer (conversion factor 0.19) (according to data provided to the EWG by the manufacturers).*

### 4.2. Quality assurance for FIT in the Dutch Colorectal Cancer Screening Programme

*Marie-Louise Heijnen, Senior Programme Manager for Introduction of CRC Screening in the Netherlands, RIVM*

CRC screening using FIT (FOB-Gold on BioMajesty analyser) for 55-75-year-olds commenced in The Netherlands in January 2014. By 2020, uptake of the screening test is expected to be 60% and uptake of follow-up colonoscopy 85% (≈72,000/85,000 positive FIT per year).

Three laboratories are employed in FIT analysis, working as one, using identical methods and configuration and with QA monitoring provided by the Dutch external QA scheme organiser. Results from internal and external QC samples are reviewed by the country co-ordinator:

- Percentage positive results > (88 ng/mL [52 µg/g])
- Percentage results below detection limit (< 20 ng/mL) [<12 µg/g]
- Percentage results > 20 and < 88 ng/mL (<52 µg/g)
- Daily average + SD calculated on the basis of binomial statistics

Information is available from www.rivm.nl/en/Topics/B/Bowel_cancer_screening_programme

### 4.3. Should we use different cut-offs for women and men in FIT?

*Isabel Portillo Villares, Cancer Detection Programmes, Bilbao*

Since 2009, biennial CRC screening has been provided to individuals aged 50-69 years using one-sample OC-SENSOR (cut-off 100 ng/mL [20 µg/g]) in the Basque Country. The programme achieved 100% coverage in 2013. Uptake (defined by analysed FIT) in 2012 was quoted as 65.3% and positivity 6.9%. A study was undertaken to investigate false-positives in women:

- The differences in results of CRC Screening Programme between women and men must be carefully considered in order to reduce false-positives in women.
- More studies should be performed to analyse the negative consequences of unnecessary colonoscopies.

- Other risk factors might be included (multivariate analysis) to improve the sensitivity and specificity of the test.

### 4.4. SCREESCO a Swedish national study on colorectal cancer screening with high sensitivity FIT and colonoscopy FIT pilot in Sweden

*Rolf Hultcrantz, Professor of Gastroenterology and Hepatology, Karolinska Institute*

Since 2008, CRC screening (FOBT + colonoscopy) has been available to the population of Stockholm. In 2011, a nationwide study was approved to assess the outcome of CRC screening in terms of disease-specific mortality and incidence, compliance with screening, the health economics and preferred screening modality.

Eighteen of the 21 counties in Sweden are participating in SCREESCO. The study population (aged 59-62 years) will comprise 20,000 individuals offered colonoscopy, 60,000 FIT and 120,000 controls. Outcomes will be assessed after 15-years of follow-up.

Each county will meet the cost of colonoscopy.

### 4.5. CRC Screening in Ibaraki Prefecture of Japan

*Yoko Saito, Japan*

Since 2007, the Ibaraki Prefecture has provided CRC screening using two-sample OC-SENSOR (cut-off 20 µg/g [100 ng/mL]).

A study was undertaken in 616,086 subjects to assess clinical outcomes (PPV and Dukes' stage) associated with the two-day sampling technique – first day positive (+/+, +/-, +/nd), first day negative (-/+) or both days positive (+/+).

- The proportions of positive FIT, cancer, and invasive cancers were 62%, 38% and 19%, respectively.
- Both days positive group (+/+) showed higher PPV for total cancer detection (6.8% vs 3.1) and for invasive cancer detection (4.3% vs 1.7%) than the first day only positive group (+/+, +/-, +/nd).

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