Barcelona 2015

8th Meeting of the Expert Working Group (EWG) – 'FIT for Screening'

Friday, 23 October 2015: 10:15–12:00

MEETING REPORT

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Expert Working Group (EWG) founding members:

- Jim Allison, University of California, San Francisco, USA (James.Allison@ucsf.edu)
- Callum Fraser, University of Dundee, Scotland (callum.fraser@nhs.net)
- Stephen Halloran, Director of the NHS Bowel Cancer Screening Southern Programme Hub (retired) and Professor Emeritus, University of Surrey, UK (s.halloran@surrey.ac.uk)
- Graeme Young, Flinders University of South Australia, Australia (graeme.young@flinders.edu.au)

The meeting was chaired by **Professor Ernst Kuipers**, Department of Gastroenterology and Hepatology, Erasmus MC, Rotterdam, The Netherlands (e.j.kuipers@erasmusmc.nl)

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

Agenda items:

1. **Welcome and Introduction** (slide set no. 1)
   Ernst Kuipers, Department of Gastroenterology & Hepatology, Erasmus MC, Rotterdam, NL
2. **The FIT Pilot in England** (slide set no. 2)
   Stephen Halloran, former Director of the NHS Bowel Cancer Screening Southern Programme Hub, Guildford, UK
3. **Development of an improved artificial matrix** (slide set no. 3)
   Oliver Devey, University Hospitals Birmingham NHS Foundation Trust
4. **Uptake, quantitative values and PPV of FIT by socioeconomic level in Barcelona** (slide set no. 4)
   Andrea Burón, Preventive Medicine Physician, Hospital del Mar, Barcelona
5. **The performance of FIT using the "HM-JACKarc" analyser to triage symptomatic patients** (slide set no. 5)
   Josep Maria Augé, Department of Biochemistry and Molecular Genetics, Hospital Clínic de Barcelona
6. **Preparation for population-based colorectal cancer screening in Iceland** (slide set no. 6)
   Sunna Guðlaugsdóttir, Consultant Gastroenterologist, The Icelandic Cancer Society
7. **A method to select FIT cut-off concentration** (slide set no. 7)
   Jayne Digby, Scottish Bowel Screening Research Unit, University of Dundee
8. **Investigation into the background of CRC patients discovered by FIT screening, 2000-2013 in Ibaraki, Japan** (slide set no. 8)
   Yoko Saito, Ibarakiken Medical Center, Mito, Ibaraki, Japan
9. **Participation, CRC detection, interval cancers and FIT results over three rounds of screening in the Basque Country** (slide set no. 9)
   Isabel Portillo, Programme Manager, Colorectal Detection Programme, Bilbao, The Basque Country
10. **Combined study for gastric and colorectal cancer screening (GISTAR) and the potential of FIT use in gut microbiome testing** (slide set no. 10)
    Mārcis Leja, Faculty of Medicine, University of Latvia

1. Introduction (slide set no. 1)

Ernst Kuipers, Department of Gastroenterology & Hepatology, Erasmus MC, Rotterdam, NL

The World Endoscopy Organization's Colorectal Cancer Screening Committee's EWG 'FIT for Screening' was founded in 2012 by Professors Graeme Young (Australia), Stephen Halloran (UK), Callum Fraser (Scotland) and James Allison (USA). The EWG meets twice a year and met for the eighth time in Barcelona on 23 October 2015. The meeting attracted about 120 delegates who heard from a selection of international speakers on new developments in FIT CRC screening around the world. The EWG's remit, publications and meeting reports are available here: http://www.worldendo.org/weo-crcsc-expert-working-group-fit-for-screening.html

2. The FIT Pilot in England (slide set no. 2)

Stephen Halloran, former Director of the NHS Bowel Cancer Screening Southern Programme Hub, Guildford, UK

In 2014, the NHS Bowel Cancer Screening Programme in England piloted use of a quantitative faecal immunochemical test (FIT) as an alternative to the guaiac-based faecal occult blood test (gFOBt). One in every 28 invitations for screening by two of the five BCSP Hubs offered a FIT (OC-SENSOR, Eiken Chemical Co. Ltd., Japan) instead of a gFOBt. During the six-month study period, 1,126,087 gFOBt and 40,930 FIT invitations were issued. The haemoglobin concentration cut-off for positivity (and subsequent referral for colonoscopy follow-up) was 20 µg Hb/g faeces. The elapsed time period between kit sent and the final result was substantially shorter (only one faecal sample is required for FIT, compared with three or more for gFOBt). Overall, uptake of screening using FIT (66.4%) was 7.1 percentage points higher than uptake with gFOBt (59.3%), indicating that use of FIT would increase the number of people screened each year by about 290,000. Uptake of screening was increased with FIT in stratified analyses – for men and women who had participated before ('incident' screening), for first-timers ('prevalent' screening), for all age-groups and across all quintiles of deprivation (there was some evidence that the increase in uptake of screening using FIT was even greater amongst more deprived cohorts). The use of a low cut-off for positivity (20 µg Hb/g faeces) allowed the investigators to evaluate colonoscopy outcomes according to higher cut-off concentrations. As a proportion of all outcomes, more cancers, high- and intermediate-risk adenomas were detected by FIT as the cut-off for positivity increased, although a high cut-off for positivity disproportionately disadvantaged women, the more elderly and previous non-responders. FIT provides an opportunity for personalised population-based screening and a contribution to a multivariate risk score for CRC.

3. Development of an improved artificial matrix (slide set no. 3)

Oliver Devey, University Hospitals Birmingham NHS Foundation Trust

The UK NEQAS (United Kingdom National External Quality Assessment Service) supports laboratory quality assurance worldwide and Birmingham Quality, one of the 26 UK NEQAS centres, has run the EQA programme for the NHS Bowel Cancer Screening Programme (BCSP) since 2012. The EQA material used for the gFOBt cards has been found to be unsuitable for FIT EQA. Efforts to improve the stability of the FIT buffer to ensure Hb stability with the addition of antimicrobial/protease inhibitors to the gFOBt EQA material or using rice flour yielded unsatisfactory results. Fixed whole blood plus antimicrobials/ protease inhibitors, however, showed excellent results. Twenty five EQA samples were produced and sent in the normal post from and to Birmingham Quality. One EQA specimen was tested upon receipt (using an HM-JACKarc FIT analyser loaned by Alpha Laboratories) and the other samples were refrigerated at 2-8°C and tested at regular intervals over the next weeks. The new buffer demonstrated excellent stability with 93% recovery of Hb after three weeks. Tests for homogeneity showed that between-sample agreement expressed as percentage CV was 5.1%. Taking into account the potential sampling error, the material appears to be suitably homogeneous. Further trialling of the new material

highlighted the importance of sample preparation, particularly the sample load on the tip of the sampling probe. It is also recommended that an hour is allowed between sampling the EQA material and analysis to allow full dispersal of the material into the buffer.

4. Uptake, quantitative values and PPV of FIT by socioeconomic level in Barcelona (slide set no. 4)

Andrea Burón, Preventive Medicine Physician, Hospital del Mar, Barcelona

The Barcelona Bowel Cancer Screening Programme (Programa de detecció precoç de càncer de còlon i recte de Barcelona) commenced in 2009 and is now in its third round of biennial screening using OC-SENSOR (Eiken Chemical Co. Ltd.) (www.prevenciocolonbcn.org). The Programme is coordinated by two hospitals (Mar and Clinic) and pharmacies act as intermediaries for the distribution of FIT kits and collection of completed kits. Hospital Clinic provides the laboratory analyses and both hospitals perform the corresponding visits and colonoscopies. The initial target of 200,000 men and women aged 50-69 is now being extended to the whole of Barcelona (about 400,000 people).

Round one uptake (43.6%) and FIT positivity (6.2%) are related to socioeconomic measures of deprivation (MEDEA index): uptake (which is higher in women) *increases* with deprivation (although the most deprived areas have the lowest uptake) and positivity (higher in men) increases with deprivation. The relationship between disease detection and deprivation is less clear, whilst colonoscopy non-compliance is higher in the most deprived (and high in the least deprived, especially women). Results for round 2 are similar (uptake 48.0%, positivity 5.2%) and other regions in Spain have reported similar results.

5. The performance of FIT using the HM-JACKarc analyser to triage symptomatic patients (slide set no. 5)

Josep Maria Augé, Department of Biochemistry and Molecular Genetics, Hospital Clínic de Barcelona

This presentation reported on a clinical evaluation of the HM-JACKarc FIT analyser (Kyowa Medex, Japan). The HM-JACKarc sample collection device collects a mean of 2.0 mg faeces, which is less than the amount collected by other FIT devices. Standardisation of the units assists comparisons between devices but further efforts are required. Evaluations in symptomatic patients are helpful and Hb concentrations below the limit of detection are useful for ruling out disease. Two hundred and eight symptomatic patients (92 men, 116 women) provided two FIT samples from separate bowel motions for HM-JACKarc analysis. The prevalence of ACRN was 18.5% in men and 10.3% in women, and about 70% of colonoscopies followed a faecal haemoglobin >0 – <10 µg/g faeces. The majority of ACRN and low-risk adenoma occurred in this group. Evaluations in symptomatic patients are useful but the higher sensitivity is a drawback. High faecal haemoglobin levels are, mainly in men, related with pathology severity and women may benefit from personalized strategies because of different bleeding patterns.

6. Preparation for population-based colorectal cancer screening in Iceland (slide set no. 6)

Sunna Guðlaugsdóttir, Consultant Gastroenterologist, the Icelandic Cancer Society

In 2002, the Director of Health in Iceland recommended annual gFOBt for all men and women aged 50+, although that recommendation was not implemented. Up to 30% of the population aged 50-59 undergoes opportunistic screening by colonoscopy and the number of colonoscopies carried out over the last decade has increased steadily in all age-groups, although the stage at diagnosis has changed little. The Icelandic Cancer Society (ICS) has been tasked with advising the Icelandic health authorities on which approach to use for an organised population-based cancer screening programme and its advice will follow the European guidelines (*i.e.* FIT). Iceland has the fourth highest life expectancy in the world (82 years); CRC survival is one of the highest in all OECD countries and CRC mortality below average. Screening adults aged 50-75 years will target approximately 86,000 individuals. Following the financial crisis in 2008 plans for organised CRC screening were suspended, although the plans have health authority and public support and the Icelandic Parliament's final decision on implementation is now

expected soon. Challenges include securing the clinical workforce required to support a screening programme.

7. A method to select FIT cut-off concentration (slide set no. 7)

Jayne Digby, Scottish Bowel Screening Research Unit, University of Dundee

An escalation in GP referrals for colonoscopy (4,225 in 2011-2012 compared with 1,216 in 2007 and without evidence of gain in CRC diagnoses) has stretched colonoscopy capacity in Scotland with a knock-on effect on the Scottish Bowel Screening Programme. After a six-month evaluation of FIT in Scotland (38,720 participants), the Scottish Government has recently approved implementation of FIT as the first-line test for CRC screening in Scotland. Use of FIT provides an opportunity to set the cut-off Hb concentration for positivity according to colonoscopy capacity as well as to consider the known associations between f-Hb and age, sex, deprivation and screening history. The use of data on interval cancers and advanced neoplasia diagnosed at subsequent screening could also be considered when selecting f-Hb cut-off concentrations.

The Scottish FIT pilot identified 31 interval cancers in FIT-negative participants. At a cut-off of 80 µg Hb/g faeces (using the OC-SENSOR DIANA analyser [Eiken Chemical Co. Ltd., Japan]), the proportion of subjects with an interval cancer in FIT-negative subjects was similar to that in gFOBt-negative subjects, and subjects with a f-Hb of 60-79.9 µg Hb/g were much more likely to have an interval cancer compared with subjects whose f-Hb was zero (undetectable) (odds ratio 24.70 [95% CI 4.89, 124.64]). Amongst participants who were positive in the next screening episode, advanced neoplasia was almost four times more prevalent in those with a previous f-Hb of 60-79.9 µg Hb/g faeces compared with those with a previous f-Hb of 0-19.9 µg Hb/g faeces (65.0% vs. 16.4% ($p < 0.001$)). Compared with the cut-off used (80 µg Hb/g faeces), a cut-off f-Hb of 60 µg Hb/g faeces could detect 17.2% more CRC and generate 25.6% more colonoscopies, whilst a cut-off f-Hb of 40 µg Hb/g faeces could detect 24.1% more CRC with 58.6% more colonoscopies. These data highlight the potential to monitor more closely those participants with consistently elevated f-Hb and, in larger cohorts, age and sex differences can also be assessed to determine if more tailored screening strategies are merited.

8. Investigation into the background of CRC patients discovered by FIT screening, 2000-2013 in Ibaraki, Japan (slide set no. 8)

Yoko Saito, Ibarakiken Medical Center, Mito, Ibaraki, Japan

In Japan CRC screening was launched as a national policy for both sexes aged over 40 years in 1992. The OC-SENSOR FIT system is used (Eiken Chemical Co. Ltd., Japan) with a cut-off of 20 µg Hb/g faeces. Participation remains poor at only 35%. Two-day FIT sampling has been widely accepted and the aim of the study presented was to investigate the background of the colorectal cancers discovered by this method. Data from 3,106 CRC cases discovered by FIT screening between 2000 and 2013 were analysed by age, sex, screening history, locations, and Dukes' staging.

Females accounted for 39.5% cases (females n=1,228; males n=1,878). Amongst female cases, 959 (78.1%) were aged 50–74 years and 436 cases (35.5%) were identified after the first-time (prevalent) screen. Intra-mucosal Dukes' A in the rectum and in the ascending colon was significantly lower in the prevalent group than in the non-prevalent group. Dukes' C in the ascending colon was significantly higher in the prevalent group than in the non-prevalent group.

Amongst males, 1,388 (73.9%) cases were aged 50–74 years-old and 749 cases (39.9%) were in the prevalent group. In the rectum and in the sigmoid colon, intra-mucosal Dukes' A was significantly lower and Dukes' B was significantly higher in the prevalent group than in the non-prevalent group. Dukes' C in the ascending colon was significantly higher in the prevalent group than in the non-prevalent group.

Comparing between females and males, in the ascending colon, intra-mucosal Dukes' A was significantly higher and Dukes' C was significantly lower in males than in females in the first-time group. For both

females and males in the prevalent group, the proportion of detected CRCs in the sigmoid colon was significantly higher and in the ascending colon was significantly lower than the non-prevalent group. The results indicate that repeated FIT screening was needed to detect CRCs in the ascending colon.

9. Participation, CRC detection, interval cancers and FIT results over three rounds of screening in the Basque Country (slide set no. 9)

Isabel Portillo Villares, Programme Manager, Colorectal Detection Programme, Bilbao, The Basque Country

The Colorectal Cancer Screening Programme of biennial FIT screening in the Basque Country was rolled out in 2009. The programme uses OC-SENSOR (Eiken Chemical Co. Ltd., Japan) at a cut-off of 20 µg Hb/g faeces and reports an uptake of 68.5% and a positivity of 6.2%. Coverage is now 100% and third round data are becoming available. During the period 2009-2014:

- participation increased significantly in all rounds by sex and age group;
- positivity decreased in successive rounds (but not by as much as expected);
- the advanced neoplasia detection rate decreased by round (rates higher in men than women);
- positivity and the proportion of lesions detected was similar between irregular (previous non-participants) and first-time participants (lower for previous participants);
- CRC staging was similar for first-time, regular (previous) and irregular (previous non-responder) participants, although a higher proportion of cancers was found in the right colon amongst regular attenders compared with the other groups.
- post FIT-negative interval cancers were more often detected in older men (60-69 years) and more than half were detected in an advanced stage;
- post colonoscopy interval cancers were more often detected in older women (60-69 years) and 52.6% were staged III-IV.

10. Combined study for gastric and colorectal cancer screening (GISTAR) and the potential of FIT use in gut microbiome testing (slide set no. 10)

Mārcis Leja, Faculty of Medicine, University of Latvia

This presentation described an ongoing prospective study to assess the benefit of *H. pylori* eradication in reducing mortality from gastric cancer, as well as to search for new biomarkers for gastric cancer and explore the potential for risk stratification. Altogether 30,000 adults aged 40-64 years will be enrolled, providing 90% study power to detect at least 35% reduction in gastric cancer mortality at 15 years of follow-up. Generally healthy general population subjects are randomised into two groups. Group 1 will undergo non-invasive testing for pepsinogen (PgI, PgII), fasting gastrin (G-17), *H. pylori*, cancer autoantibodies, volatile markers for gastric cancer in the breath and will complete a FIT kit. Group 2 (controls) will complete a FIT kit. *H. pylori*-positive participants will receive eradication therapy. In Group 1, pepsinogen-positive participants, those positive for cancer-related autoantibodies and/or volatile markers for gastric cancer will be referred for an upper endoscopy. All FIT-positive participants (Groups 1 and 2) will be referred for colonoscopy. Endoscopy follow-up will follow MAPS (Management of precancerous conditions and lesions in the stomach) guidelines (1). The outcome will be mortality from gastric cancer at 15+ years.

Since October 2013, and to date (22 October 2015), 1,606 participants had been allocated to Group 1 and 1,607 to Group 2 (total 3,213); 863 endoscopies have been performed and *H. pylori* eradication delivered for 617 participants. FIT positivity (both Groups) has been 5.7% (119 colonoscopies). Amongst participants who have had an endoscopy, 3.92% had intestinal metaplasia (Operative link on gastric

intestinal metaplasia assessment [OLGIM] staging III-IV), 5.86% low-grade dysplasia (LGD), 3.14% an indefinite outcome for dysplasia and 0.39% adenocarcinoma.

A pilot study has been performed to test for faecal microbiota stability being preserved in the OC-SENSOR FIT buffer bottle. The preliminary data indicate that this could be a reliable medium for preserving faecal microbiota for a few days or even 1-2 weeks. This could provide an excellent microbiota study tool for wide epidemiological studies.

Reference

1. Dinis-Ribeiro M, Areia M, de Vries AC, Marcos-Pinto R, Monteiro-Soares M, O'Connor A, et al. Management of precancerous conditions and lesions in the stomach (MAPS): guideline from the European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter Study Group (EHSG), European Society of Pathology (ESP), and the Sociedade Portuguesa de Endoscopia Digestiva (SPED). Endoscopy. 2012;44(1):74-94.