World Endoscopy Organization
Colorectal Cancer Screening Committee

UEGW, Amsterdam 2012

2nd Meeting of the Expert Working Group (EWG) – 'FIT for Screening'

Friday,October 19, 2012: 09:00-11:30 hrs

MEETING REPORT

Summary of decisions reached previously by the EWG supported by consensus of those present at the previous meeting

1. Nomenclature
   - Faecal immunochemical test ***for haemoglobin*** (abbreviated as 'FIT').
2. FIT descriptions
   - The analytical technique is '**immunochemical'** and not 'immunological'.
   - Use of the term '**immunoturbidimetry'** is more appropriate than 'latex agglutination'.
   - Inclusion of '..**for haemoglobin'** in the full FIT description.
   - Avoid using FIT^{50}, FIT^{100} and similar descriptions when detailing faecal haemoglobin cut-off concentrations used since the analytical and clinical characteristics of a single cut-off are likely to be very different in different devices/systems.
3. Reporting units
   - µg haemoglobin/g faeces – full adoption can be achieved once we have identified and adopted standardised methods for determining sample mass and buffer volume.
4. Traceability of haemoglobin standard
   - All manufacturers should use a WHO traceable standard and the recommended spectrophotometric cyanmethaemoglobin method to assign the haemoglobin concentration of calibrators used in all FIT assays.

Summary of new EWG recommendations and continuing activities

1. FIT Publications: as a guide for reviewers, authors and journal editors, EWG will progress the development of a WEO-endorsed document which describes the essential analytical content of FIT-related medical and scientific papers. The revised EWG document will be prepared for discussion at the next meeting in Orlando (17 May 2013).
2. FDA approval of quantitative FIT: The EWG will continue in its efforts to engage with the FDA and would be grateful for contributions to this effort from FIT manufacturers.
3. IQC/EQA: EWG to provide guidance on quality management of FIT laboratory testing to encourage acceptable analytical performance in colorectal cancer screening programmes. EWG to advise what IQC/EQA information should be included in tender documents.

4. Procurement: The EWG will prepare a document to provide guidance on procurement of FIT systems (Discussion Document no. 6).

5. The WEO will prepare a website where documents relevant to the activities of the FIT for Screening EWG will be made available:

   These documents will include;

   - EWG FIT for Screening remit
   - EWG Discussion Documents
   - EWG meeting summaries
   - EWG FIT procurement guidelines
   - EWG guidance on desirable content of publications on FIT for reviewers, authors and editors
   - EWG guidance on quality management of FIT laboratory testing
   - FIT questionnaire and survey of FIT manufacturers – most recent update
   - EWG Reference documents
     - Listing of FIT publications (reference document no. 1)
     - Listing of population-based colorectal cancer screening programmes worldwide (reference document no. 2).

Progress since first EWG meeting in San Diego, May 2012

Professor Callum Fraser outlined the EWG-led initiatives to raise the profile of FIT amongst clinical biochemists through the American Association for Clinical Chemistry and Laboratory Medicine (AACC):

- Article in the AACC newsletter: Fraser CG. Fecal occult blood tests. Life savers or outdated colorectal screening tools? Clinical Laboratory News 2011;37:8-10.(http://www.aacc.org/publications/cln/2011/march/Pages/FecalOccult.aspx)
- AACC Online Lecture Library: Colon Cancer: The role of fecal tests. (http://www.aacc.org/development/webcasts/lecture-library/pages/default.aspx)
- NACB Blog – Has quantitative measurement of fecal hemoglobin concentration come of age? (http://www.aacc.org/members/nacb/NACBBlog/lists/posts/post.aspx?ID=44)
- AACC Annual Meeting, Los Angeles, 2012: 90 minute Short Course on 'Newer fecal tests: opportunities for professionals in laboratory medicine'.
- Editorial: Fraser CG, Allison JE, Young GP, Halloran SP. Newer fecal tests: opportunities for professionals in laboratory medicine. Clinical Chemistry 2012;58(6) (http://www.clinchem.org/content/58/6/963.full.pdf) and podcast (http://www.aacc.org/publications/clin_chem/podcast/Documents/ClinChem201206_Fraser.pdf).
- Forthcoming webinar (23 February 2013) – New developments in colorectal cancer screening.

Publications involving FIT (Discussion Document No. 5)

To facilitate comparison of FIT performance, the EWG has recognised the need for full descriptions of pre-analytical (handling and storage) and analytical (*e.g.* assay imprecision and reportable range) characteristics of FIT used in studies to be documented in articles submitted for publication.

Professor Callum Fraser drew attendees' attention to the guidance currently available from the Consortium of Laboratory Medicine Journal Editors (1), STARD (STAndards for the Reporting of Diagnostic accuracy studies [http://www.stard-statement.org/]) and the EWG Discussion Document no. 5 (circulated previously).

The EWG recommendations for fully characterising and describing FIT in published articles were presented for discussion and Professor Fraser stressed the need to engage with authors, reviewers, journal editors and publishers to ensure an understanding of the need for this information.

EWG will produce guidance on the use and interpretation of manufacturers' information about products (certainly *imprecision* of analysis is usually missing).

The EWG will develop guidance for authors, reviewers and journal editors on the minimum amount of pre-analytical and analytical information (a **minimum dataset** [MDS]) that would be acceptable about FIT product(s) and performance characteristics.

The EWG will consider how best to ensure that journals include at least the MDS of FIT information with published materials – and perhaps additional information as supplemental files commonly used by journals at present.

Professor Graeme Young suggested that a paper might be prepared by the EWG to ensure that journal editors understand why the MDS is needed.

Journal editors should ensure that authors identify the generation of analytical tests described.

EWG will produce a document as a guide to reviewers, authors and journal editors that will be given WEO accreditation. The EWG document will be prepared for discussion at the next meeting in Orlando (17 May 2013).

FDA approval of quantitative FIT

Professor Halloran outlined his understanding of the FDA's current position on quantitative FIT, which was that, because pre-analytical *faecal sampling* is not *quantitative*, then the test cannot be considered *quantitative*. Whilst this mitigates against use of such FIT analytical systems as a diagnostic test for individuals, it is currently unclear why the proven value of FIT in population screening has not been recognised and quantitative FIT technology not endorsed by the FDA for this purpose.

It was thought that one important obstacle to getting FDA approval for quantitative devices is the cost of acquiring sufficient new US data. The FDA is understood to require RCT data (FIT vs colonoscopy) generated on a US population and on the use of at least two competitive FIT systems.

The EWG will continue in its efforts to engage with the FDA and would be grateful for contributions to this effort from FIT manufacturers.

Manufacturers were asked to keep the EWG informed of any developments regarding FDA approval of quantitative devices.

Units of reporting

Professor Callum Fraser reiterated the EWG advice that FIT reporting units should be **µg Hb/g faeces**. The EWG will progress with efforts towards achieving a standardised method for defining the mass of faeces collected and the volume of buffer.

The meeting heard that evidence supports the positive progress that manufacturers have made toward to accepting the principle of standardisation of reporting units.

Professor Halloran informed the meeting that a FIT evaluation study that will commence shortly at the English NHS Bowel Cancer Screening Programme's Southern Hub and there is a need to have methods available for assessing sample stability and faecal mass. A report from the study will be available for discussion at the next UEGW meeting in Berlin 2013.

Quality assurance (Discussion Document No. 4)

Professor Callum Fraser reiterated one of the recommendations made in the 1999 Stockholm Consensus Statement on 'Strategies to set global quality specifications in laboratory medicine' that published professional recommendations from international expert bodies to progress efforts toward quality of analytical tests. Thus, the EWG should take on the task of advising on how good FIT analysis should be in terms of reproducibility and comparability across analytical systems in order to provide clinical data of the quality required.

EWG recommendations:

- Samples used for IQC should mimic samples received from screening participants.
- Every FIT result should be associated with a measure of analytical quality.
- IQC must be instituted in all settings in which FIT analyses are performed, whether qualitative or quantitative.
- EQA systems need urgent development as new screening programmes are being planned and implemented around the world.
- EQA should reflect what is done in ***real*** clinical practice and should facilitate comparison of FIT data over time and geography.
- EQA/IQC issues need to be covered in countries' tender documents.

EWG to provide guidance on quality management of FIT laboratory testing to ensure acceptable analytical performance in colorectal cancer screening programmes.

EWG to advise what information should be included in tender documents.

Manufacturer questionnaires

Dr Seaman stated that the EWG was very grateful to those manufacturers that responded to the request for information and encourages the manufacturers to continue dialogue to ensure that information is kept up-to-date.

It was suggested that a live document be uploaded to a WEO supported website, although issues with version control and medico-legal considerations need to be addressed.

A report is being prepared detailing the questionnaire data, although the meeting recognised the problem of maintaining up-to-date data.

Procurement of FIT systems (preparation of Discussion Document No. 6)

The EWG will prepare a document to provide guidance on procurement.

The EWG recognises the need for manufacturers to provide a subset of information in tender documentation that is relevant to each country. In preparing the procurement guidance, the EWG would be grateful for help from manufacturers and those in attendance with procurement experience.

Summary of presentations

1. 'External Quality Assessment for automated FIT'

Mr WataruIkezaki, Eiken Chemical Co. Ltd, Japan
(Wataru_Ikezaki@eiken.co.jp)

Mr Ikezaki provided an overview of the 'Eiken Quality Assessment Service' (EQAS) for OC-Sensor that commenced in July 1995. The EQAS provides more than 1,000 facilities in ten countries with annual information about the relative bias of their measurements. Two samples* of unknown haemoglobin concentration are sent from the manufacturer to each OC-Sensor user facility: each sample is analysed three times on each of two days and the results are reported to Eiken. Eiken plots the (average of) results** for each facility on a graph and users are then informed of the relative bias of their measurements compared with results from other users. Liquid samples replaced lyophilized samples in 2008 with a consequent reduction in variation about the mean.

Questions/comments

**The material used is the same as that provided for internal quality control of systems marketed by this company.*

*** The average of the six measurements for each user is plotted on the graph and Professor Callum Fraser pointed out that use of average measurement would make the imprecision **smaller** by √6, so the performance reported is superior to that actually achieved with specimens provided by participants in screening programmes.*

2. 'FIT in France'

Dr Lydia Guittet, Inserm, France
(guittet-l@chu-caen.fr)

Dr Guittet outlined the FIT studies conducted in France over the last ten years (involving more than 161,000 individuals), with particular note about the results of comparative studies including IGOR (MagStream HT, OC-Sensor, FOB Gold) and HeMO (OC-Sensor, MagStream). The importance of RCT or paired-design studies was emphasised.

The use of guaiac-based FOB (gFOBT) for colorectal cancer screening commenced in France in 2006 and by 2008 extended country-wide*. FIT was recommended for use in 2008 and a governmental decision has been made in 2012 to move to one-sample FIT in 2013. Currently FIT (two samples: MagStream) is being used for screening in one Department in France (Calvados).

Questions/comments

**Uptake with gFOBT is < 50% and efforts are being made to improve this by raising awareness.*

3. 'A Tale of Two Countries: Screening Data Using Two Analytical Systems'

Mr Yasunobu Masuda, Kyowa Medex Co. Ltd, Japan
(yasunobu.masuda@kyowa-kirin.co.jp)

Mr Masuda presented data on two studies comparing two quantitative FIT - Kyowa's HM-Jack and Eiken's OC-Sensor. The first study was conducted in a Taiwanese screening population from 2010 in more than 120 hospitals. There were differences between the two products in terms of positivity and disease detection, although it was noted that differences could not be evaluated objectively because the study cohorts were different. The second study was conducted in Florence (2) amongst 10,000 individuals. The investigators tested one faecal sample for each participant simultaneously with the two different FIT. Clinical outcomes were compared for 306 individuals with a positive test result from either HM-Jack or OC-Sensor. There were clear differences between the clinical outcomes attained with the two systems, even when the data were adjusted to the same cut-off faecal haemoglobin concentration.

Questions/comments

These studies highlighted the difficulties in trying to compare different FIT analytical systems based on somewhat different principles. The lower the cut-off faecal haemoglobin concentration used and the greater the test positivity, the more colonoscopies will be performed and more disease will be detected but with the drawback of lower sensitivity and more false positive results.

4. Ten years' experience in Japan: CRC screening test in Ibaraki prefecture

Dr Y Saito, Ibaraki Medical Centre, Mito, Ibaraki, Japan
(c/o takuo_ichiyanagi@eiken.co.jp)

Dr Saito described the observations made when a new buffer was introduced in 2006 to the 2-day FIT sampling method (OC-Sensor) used in the Ibaraki prefecture amongst men and women aged 40+ years (cut-off concentration of 100ng/mL – equivalent to 20 µg Hb/g faeces). In the years preceding 2006, the investigators found some significant differences year-on-year in test positivity and positive predictive values for cancer. After the introduction of the new buffer in 2006, those differences were largely eliminated. The investigators concluded that the new buffer improved sample stability, although further studies are warranted.

Questions/comments

It is known that many factors influence positivity (e.g. age, sex, pathology) and what is needed is a multivariate analysis incorporating all factors including buffer characteristics to try and establish the impact of the buffer in influencing positivity. It was also noted that the changing of crucial components of any analytical system, such as the buffer, could affect the clinical outcomes over time with what was ostensibly one system. This supported the view, expressed earlier that publications should detail the exact analytical system used in reports submitted for publication including the generation of components.

5. FIT for screening Sentinel: the buffer H story

Dr Maria Chiara Anelli, Sentinel Diagnostics, Italy
(MariaChiaraAnelli@sentinel.it)

Dr Anelli's presentation described how, in 2009, Sentinel introduced a new buffer in an effort to improve sample stability. Studies using the new buffer in France have been published (Faivre *et al* (3, 4)) and Sentinel is currently conducting an evaluation study in Padova University (poster presentation at Italian Society of Clinical Biochemistry Congress in November 2012). Sentinel will present their data at a workshop at the IFCC-EFLM EuroMedlab Congress in Milan in 2013.

6. Multivariate risk scores: exploiting the potential of FIT

Professor Stephen Halloran, NHS Bowel Cancer Screening Programme, UK
(s.halloran@nhs.net)

Professor Halloran explained how the current assessment of quantitative FIT test results that assumes a positive or negative test result according to a single pre-defined cut-off faecal Hb concentration means that valuable information about the actual Hb concentration of any particular individual is wasted. Professor Halloran suggested that FIT concentrations could be used alongside the known risk factors for bowel pathology and factors that affect Hb concentrations (age, sex, screening history, geo- and socio-demographics, family history and lifestyle) to generate a multivariate risk score. The risk score could provide a better discriminator to aid population-based screening decisions about whether or not individuals should be referred for colonoscopy.

References

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2. Rubeca T, Peruzzi B, Confortini M, Rapi S. Overall evaluation of an immunological latex agglutination system for fecal occult blood testing in the colorectal cancer screening program of Florence. The International Journal of Biological Markers 2012;27:195-202.
3. Faivre J, Dancourt V, Denis B, Dorval E, Piette C, Perrin P, et al. Comparison between a guaiac and three immunochemical faecal occult blood tests in screening for colorectal cancer. European Journal of Cancer 2012;48(16):2969-76. Epub 2012/05/11.
4. Faivre J, Dancourt V, Manfredi S, Denis B, Durand G, Gendre I, et al. Positivity rates and performances of immunochemical faecal occult blood tests at different cut-off levels within a colorectal cancer screening programme. Digestive and Liver Disease: Official Journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver 2012;44(8):700-4. Epub 2012/05/01.