



New Developments in Colorectal Cancer Screening

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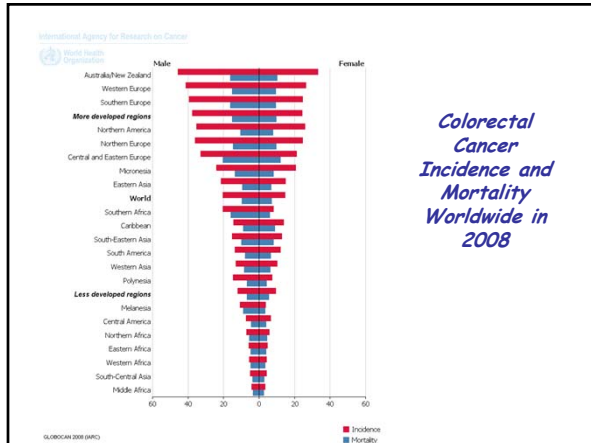
Educational Objectives

After this session, you should:

- **appreciate the need for screening for colorectal neoplasia and the role of fecal tests in screening,**
- **be able to list the advantages and disadvantages of guaiac-based FOBT, FIT, and quantitation of fecal hemoglobin,**
- **recognize that fecal hemoglobin concentration is related to both disease severity and risk,**
- **appreciate that there are still many controversies about best use of FIT in screening programs, and**
- **be able to contemplate the potential roles of FIT other than in screening.**

***Colorectal Cancer -
An Important Health Issue***

- **Worldwide, it is the third most common cancer in men after lung and prostate, and the second in women after breast,**
- **the majority of cases occur in developed regions,**
- **incidence and mortality is substantially higher in men than in women, and**
- **significant colorectal neoplasia (advanced adenomatous polyps and cancer) mostly occurs in individuals over the age of 50 years.**

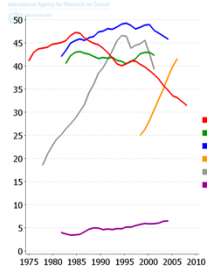


*Colorectal
Cancer
Incidence and
Mortality
Worldwide in
2008*

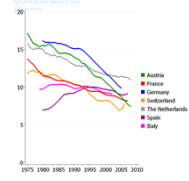
Colorectal Cancer in the US (CDC)

- **Of cancers affecting both men and women, colorectal cancer is the second leading cancer killer in the United States. In 2008, 142,950 people were diagnosed with colorectal cancer, and 52,857 people died from it.**
- **Colorectal cancer almost always develops from pre-cancerous polyps in the colon or rectum.**
- **Screening can find pre-cancerous polyps, so that they can be removed before they turn into cancer. Screening can also find colorectal cancer early, when treatment works best.**

CRC Incidence and Mortality



Incidence and mortality are falling in US and some other countries – screening/lifestyle?



<http://globocan.iarc.fr/factsheets/cancers/colorectal.asp>

Screening Modalities

- Several different screening tests are available. Each can be used alone. Sometimes they are used in combination with each other.
- As one (only) example guideline, the US Preventive Services Task Force (USPSTF) recommends colorectal cancer screening for men and women aged 50–75, using high-sensitivity fecal occult blood testing (FOBT), sigmoidoscopy, or colonoscopy.
- Talk to your doctor about which test or tests are right for you. The decision to be screened after age 75 should be made on an individual basis.

www.cdc.gov/cancer/colorectal/pdf/Basic_FS_Eng_Color.pdf

Non-Invasive Tests

- Fecal Occult Blood Testing – “two types”
- Fecal DNA
- Fecal RNA
- Fecal Proteins – M2-PK, calprotectin, CEA
- Blood – DNA, RNA, proteins

Imperiale T. Dig Dis 2012;30(Suppl 2):16-25

**CLINICIAN'S REFERENCE:
FOBT FOR CRC SCREENING**

This provides state-of-the-science information:
<http://ncct.org/wpcontent/uploads/FOBTCliniciansReferenceFinal.pdf>

- Colorectal cancer screening with FOBT has been shown to decrease both incidence and mortality in randomized controlled trials.
- High-sensitivity FOBT detect colorectal cancer at relatively high rates.
- Modeling studies suggest that the years of life saved through a high-quality FOBT screening program are essentially the same as with a high-quality colonoscopy-based screening program.

**CLINICIAN'S REFERENCE:
FOBT FOR CRC SCREENING**

- Access to colonoscopy and other invasive tests may be limited or non-existent for many patients.
- In addition, some adults prefer less invasive tests.
- All of these elements make FOBT a reasonable choice for patients.
- Recent advances in stool blood screening include the emergence of new tests and improved understanding of the impact of quality factors on testing outcomes.

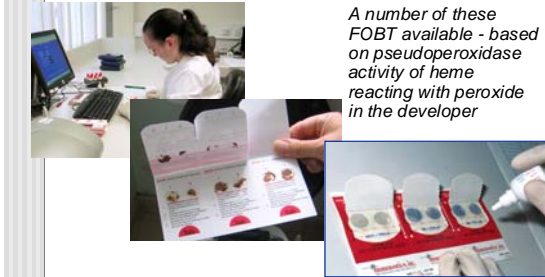
Fecal Tests

- **gFOBT** – traditional guaiac based (low sensitivity) fecal occult blood tests
- **sFOBT** – high sensitivity guaiac-based fecal occult blood tests
- **FIT** – fecal immunochemical tests for hemoglobin

Do not use the generic term FOBT and do not use iFOBT or immunological.

Expert Working Group on FIT, Colorectal Cancer Screening Committee, World Endoscopy Organization – see Gastroenterology 2012;142:422-4.

Guaiac-based FOBT



A number of these FOBT available - based on pseudoperoxidase activity of heme reacting with peroxide in the developer

Evidence for gFOBT in Screening

We identified nine articles concerning four randomized controlled trials and two controlled trials involving over 320,000 participants with follow-up from 8 to 18 years.

Combined results from the four eligible randomized controlled trials shows that participants allocated to screening had a 16% reduction in the relative risk of colorectal cancer mortality.

Hewitson P, et al. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (Hemoccult): An update. Am J Gastroenterol 2008;103:1541-9.

Guaiac-based FOBT

Some Advantages:

- *inexpensive*
- *easy to give out or to mail and to return in mail*
- *easy for people to do – although may be unpleasant*
- *stable – but ONLY once dry – MUST use the cards*
- *analytical characteristics well documented*
- *integral “performance monitor” and EQAS/PT in some countries*
- *original evidence from RCT is for traditional guaiac-based FOBT - and much evidence that the RCT results are mirrored in practice*

Guaiac-based FOBT

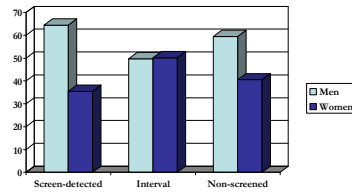
Many Disadvantages:

- multiple samples required
- many false positives and negatives
- potential for interference from meat, certain vegetables [not if delay in development], aspirin, NSAID, warfarin, vitamin C
- detect bleeding from stomach, small and large intestine
- not easy to interpret colours
- cannot be "automated"
- cut-off point set by manufacturer – so positivity rate - and colonoscopy demand – and clinical outcomes - set by manufacturer

Interval Cancers in Scotland

Cancers	Round 1	Round 2	Round 3
Screen-detected	535	208	139
Interval	193	213	229

Steele RJC, et al. Gut 2012;61:576-81



gFOBT v FIT

	Sensitivity for cancer	Sensitivity for adenomas
gFOBT	13% – 50%	8% – 20%
FIT	55% – 100%	15% – 44%

These differences are so significant that screening guidelines now specify that gFOBT and similar older guaiac tests should no longer be used.

Similar statements on gFOBT throughout the recent literature – all most recommend FIT – few sFOBT!

sFOBT are very much less studied than gFOBT and the disadvantages associated with guaiac-based tests do not seem minimised.

Fecal Immunochemical Test

- detect intact hemoglobin and early degradation products with antibodies (monoclonal/polyclonal)
- generally easier to collect - one sample only usual
- no dietary interference
- aspirin, NSAID and anti-coagulants – beneficial
- more specific for lower GI bleeding
- more analytically sensitive than gFOBT
- many publications and now trials against gFOBT
- advocated in many publications and most modern guidelines - for asymptomatic population screening

See: Rabeneck L, et al. Can J Gastroenterol 2012;26:131-47.

FIT Types

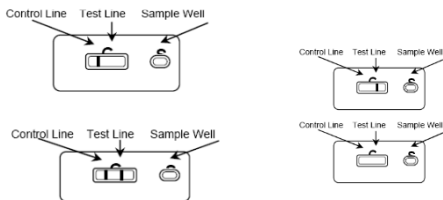
1. **Qualitative** - positive/negative – usually sample collected onto card or via probe or stick – then into buffer tube – then immunochromatographic test cassettes or strips.

Cut-off concentration for further investigation, usually colonoscopy, set by manufacturer.

2. **Quantitative** - measure fecal hemoglobin [Hb] concentration – usually automated immuno-turbidimetry.

Great advantage is that cut-off fecal hemoglobin concentration can be selected by user.

Qualitative FIT analysis



Advantages of Qualitative FIT

- usually have in-built quality control
- said to be simple to use and simple to interpret “lines” that appear
- BUT more expensive, more time-consuming, visual interpretation, lot-to-lot variation

Are these “point-of care tests”? If so, why do all involved in their use not follow established local, regional, national, and international guidelines such as for glucose, cholesterol, etc? Follow

ISO 22870:2006 – Point-of-care Testing (POCT) Requirements for quality and competence.

Fecal Immunochemical Tests - FIT

Qualitative FIT – positive/negative results



Are all qualitative FIT the same? Which is “best”?

Are FIT data transferable over time and geography?

Comparison of 6 Qualitative FIT

FIT	Positivity (%)	Sensitivity (%)	Specificity (%)
A	6.4	29.8	96.7
B	11.0	30.5	92.9
C	22.3	53.2	84.8
D	24.1	56.0	82.0
E	35.0	59.6	70.2
F	46.8	73.4	58.8

1330 patients prior to colonoscopy
 Brenner H, et al. J Cancer 2010;127:1643–9

Comparison of 6 Qualitative FIT

FIT	Positivity (%)	Sensitivity (%)	Specificity (%)	Cut-off (ng Hb/ml)
A	6.4	29.8	96.7	50 4
B	11.0	30.5	92.9	40 3
C	22.3	53.2	84.8	10 1
D	24.1	56.0	82.0	40 3
E	35.0	59.6	70.2	50 4
F	46.8	73.4	58.8	25 2

1330 patients prior to colonoscopy
 Brenner H, et al. J Cancer 2010;127:1643-9
 Cut-off data from: Hundt S, et al. Ann Intern Med 2009;150:162-9 .

Conclusions

- Qualitative FIT do not give the same outcomes
- Different ADL.
- Most use units of ng Hb/ml buffer.
- Different masses of feces in different volumes of buffer – ng Hb/ml in different FIT are not the same.
- Current units most often used for describing the ADL confound comparison of current data.

Improving Transferability of Data

The mass of feces picked up in any particular collection device should be documented [with CI].
 The volume of buffer, if tubes are used as collection devices, should be documented [with CI].

Then, mass of hemoglobin per mass of feces is known:

$$\mu\text{g Hb/g feces} = \frac{(\text{ng Hb/mL} \times \text{mL of buffer})}{(\text{mass of fecal sample in mg})}$$

Fraser CG, et al. J Natl Cancer Inst 2012;104:810-4.

Faecal Immunochemical Test

- **Qualitative FIT and Quantitative FIT.**

- **A number of analytical systems.**

OC-Sensor (Eiken Chemical Co., Japan)
 HM-JACKarc (Kyowa Medex, Japan)
 NS-Plus (Alfresa Pharma Corp., Japan)
 FOB-Gold (Sentinel Diagnostics, Italy)

- **Many advantages – the principal is that fecal hemoglobin concentration can be measured.**

Going to a "FIT 50" Strategy

System	ng Hb/mL	mg feces	mL/buffer	µg Hb/g
OC-Sensor	50	10	2.0	10
HM-JACK	50	0.5	1.25	125
SENTiFOB	50	10	1.7	8.5

The concentration [in ng Hb/mL] is unique to the device or system. Use of ng Hb/mL leads to lack of transferability and confusion.

Should use µg Hb/g feces for all reporting.

Quantitative FIT

Many studies from around the world do state that FIT are better than gFOBT in asymptomatic population CRC screening.

- **Dancourt V, et al. Eur J Cancer 2008;44:2254-8. Immunochemical faecal occult blood tests are superior to guaiac-based tests for the detection of colorectal neoplasms.**
- **van Rossum LG, et al. Gastroenterology 2008;135:82-90. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population.**
- **Hol L, et al. Screening for colorectal cancer: randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy. Gut 2010;59:62-8.**

Comparison of gFOBT and FIT

- 20,623 individuals, 50-75 years of age, randomized to either gFOBT (Hemoccult-II) or FIT (OC-Sensor).
- 10,993 tests returned: 4836 (46.9%) gFOBT and 6157 (59.6%) FIT – note uptake rates!
- 2.4% positive gFOBT versus 5.5% for FIT. Cancer and advanced adenomas were found, respectively, in 11 and 48 of gFOBT and in 24 and 121 of FIT
- gFOBT significantly underestimate advanced adenomas and cancer compared with FIT.

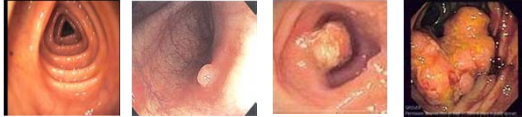
Comparison of gFOBT, FIT, FS

- The participation rate (n = 15 011, aged 50-74 years) was 49.5% for gFOBT, 61.5% FIT and 32.4% for FS screening.
- gFOBT was positive in 2.8%, FIT in 4.8% and FS in 10.2%.
- The detection rate of advanced neoplasia was significantly higher in the FIT (2.4%) and the FS arm (8.0%) than the gFOBT arm (1.1%).
- FS demonstrated a higher diagnostic yield of advanced neoplasia per 100 invitees (2.4) than gFOBT (0.6) or FIT (1.5) screening.

Many Publications on FIT

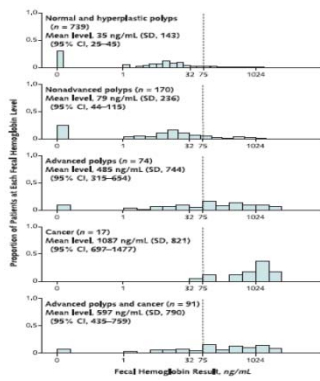
- Most studies from around the world use the quantitative FIT test as a simple qualitative test – positive or negative.
- Many use the cut-off fecal hemoglobin concentration suggested by the manufacturer.
- At present – generally only ONE cut-off fecal hemoglobin concentration to decide referral for colonoscopy.
- Is there evidence to go further and add value to this investigation?

Hemoglobin in Feces



Normal → Low risk adenoma → High risk adenoma → Cancer

Hemoglobin →



Levi Z, et al.

A quantitative immunochemical fecal occult blood test for colorectal neoplasia.

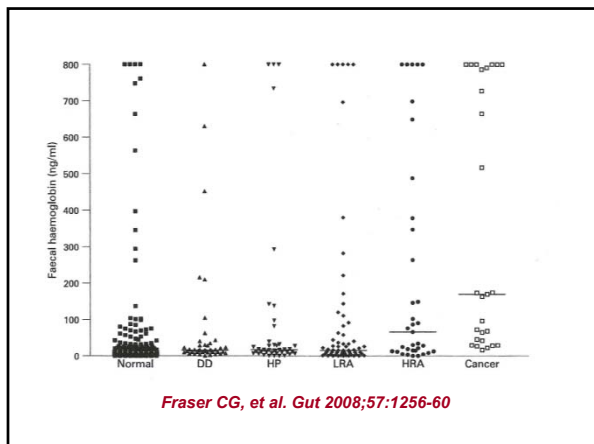
Ann Intern Med 2007;146:244-55.

1000 consecutive ambulatory patients at increased risk for colorectal neoplasia or symptomatic.

Fecal Hemoglobin and Disease

- 191 colorectal cancers and 890 adenomas detected at colonoscopy in 2597 FIT positives.
- A higher f-Hb concentration was significantly associated with male sex ($P < 0.003$) and age ($P < 0.02$). Among adenomas, higher faecal Hb content was significantly associated with size ($P < 0.0000$), presence of severe dysplasia ($P < 0.0001$) and presence of villous component ($P < 0.0002$).
- f-Hb is significantly higher for those lesions (cancer and high-risk adenomas) screening is aimed at detecting.

Ciatto S, et al. Br J Cancer 2007;96: 218-21

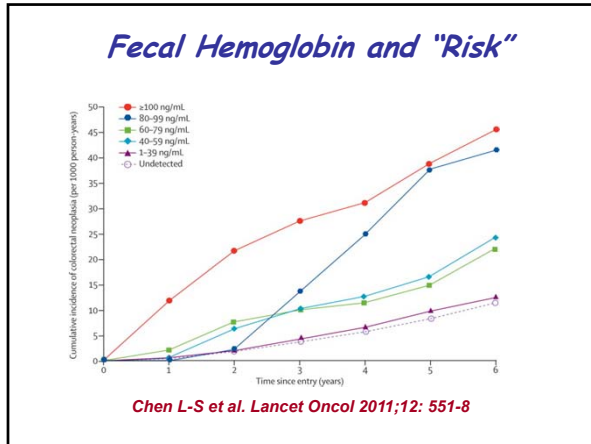


FIT at Different Cut-offs

ng Hb/mL	Positivity	DR - C + AA	PPV - C + AA	Specificity - C
<i>FIT 50</i>	6.1	3.7	49	92.9
<i>FIT 75</i>	5.7	3.2	58	95.0
<i>FIT 100</i>	4.8	3.0	63	95.8
<i>FIT 125</i>	4.1	2.7	68	96.3
<i>FIT 150</i>	4.0	2.7	71	96.6
<i>FIT 175</i>	3.6	2.6	75	97.0
<i>FIT 200</i>	3.5	2.5	74	97.1

Hol L, et al. Br J Cancer 2009;100:1103-10

- ### *Fecal Hemoglobin and "Risk"*
- **Quantitative fecal hemoglobin concentration predicts subsequent risk of incident colorectal neoplasia.**
 - **Risk stratification based on fecal hemoglobin could help clinicians, with particular attention being paid to those with higher initial fecal hemoglobin concentrations, especially those just under the threshold (usually) taken to indicate presence of colorectal neoplasia.**
- Chen L-S, et al. Lancet Oncology 2011;12: 551-8*



- ### Some Controversies?
- **How many samples should be collected?**
 - **Should there be different screening intervals?**
 - **Should aspirin, NSAID and anti-coagulants be stopped?**
 - **What cut-off fecal hemoglobin concentration should be used – one or more?**
 - **What age should screening using FIT begin?**
 - **Do "risk scores" have advantages?**
 - **Which FIT is "best"?**

- ### Number of Samples
- Guittet L, et al. [Colorectal cancer screening: why immunochemical faecal occult blood test performs as well with either one or two samples](#). *Dig Liver Dis* 2012;44:694-9.
 - Oort FA, et al. [Double sampling of a faecal immunochemical test is not superior to single sampling for detection of colorectal neoplasia: a colonoscopy controlled prospective cohort study](#). *BMC Cancer* 2011;11:434

FIT at Different Intervals

	After 1 year	After 2 years	After 3 years
Uptake (%)	63.2	61.0	62.0
Positivity (%)	5.4	6.6	5.8
Advanced neoplasia (%)	1.9	2.1	1.7

Van Roon, AH, et al. Gut. 2012 Mar 2. [Epub ahead of print]

FIT and Aspirin

1979 participants who were having screening colonoscopy and collected faeces before preparation for colonoscopy; 12% regularly used low-dose aspirin (mean age 65 y, 72% men) and 88% had never used (mean age 62 y, 54% women).

Aspirin	Sensitivity	Specificity
Yes	71%	86%
No	36%	89%

Brenner H, et al. JAMA 2010;304:2513-20.

One Cut-Off Concentration Age and Gender

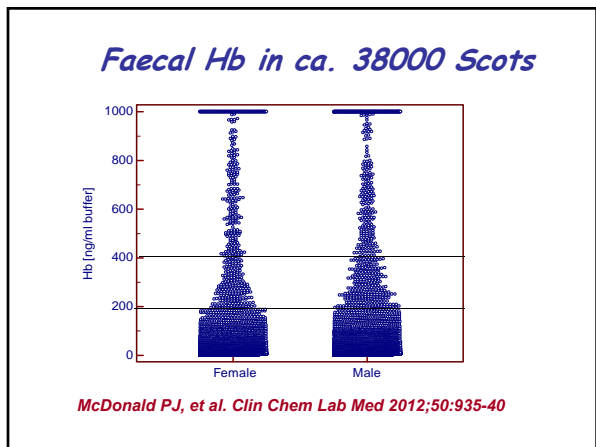
Scotland uses a gFOBT/FIT screening approach at present but plans to move to quantitative FIT.

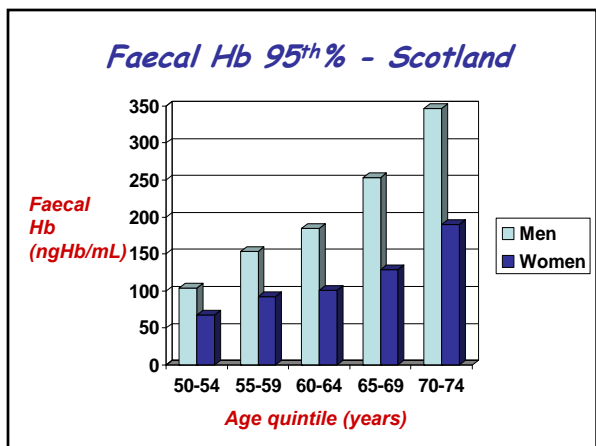
Feasibility evaluation done for 6/12 in 2 of 14 NHS Boards.

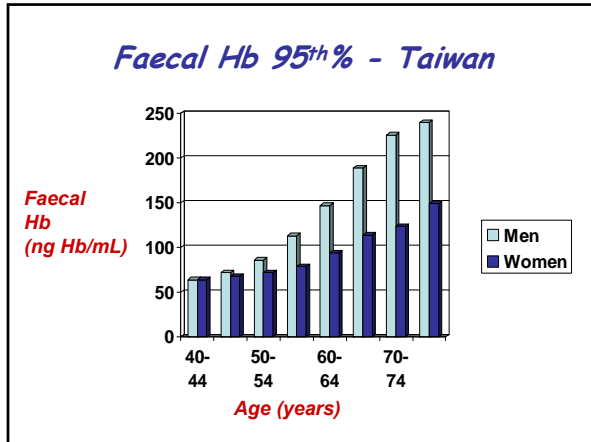
Invitations : 66225
 Returned kits: 40125
 Testable kits : 38720

Overall response rate – 60.6%
 Definitive result – 58.5%
 Overall uptake (Scotland) - 53.7%









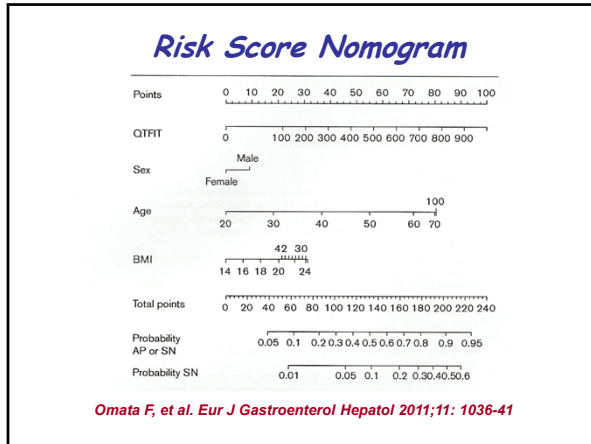
Brenner H et al.
Am J Gastroenterol 2010;105:2457-64.

At any cut-off, the sensitivity and positive predictive value were substantially higher, and specificity and negative predictive value were substantially lower, among men than women.

There are major sex differences, which might require careful attention in the interpretation of test results, and in the design, modelling, and evaluation of CRC screening strategies.

Khalid-de Bakker CA et al.
Cancer Prev Res 2011;4:1563-71.

- Mean fecal hemoglobin in FIT positives was significantly lower for women v men and for younger v older (≥55 years) subjects.
- Sensitivity (at a single cut-off Hb concentration of 50 ng Hb/ml) –
 - 5.3% in women v 26.3% in men
 - 9.5% in younger v 23.5% in older subjects.
- **This points to the need for more tailored screening strategies.**



Participants are Different

- *It is clear that one test does not fit all.*
- *There is an opportunity to develop bowel screening to address gender and age differences and tailor algorithms to individuals according to risk.*
- *There is the opportunity to make women more equivalent to men, not reduce the effectiveness in men – with quantitative FIT that measure fecal hemoglobin.*
- *Methods for measurement of fecal hemoglobin concentration are needed – everywhere!*

Numbers YOU Might Know

Why not your fecal haemoglobin?

The collage includes:

- A person's feet on a white scale.
- A blood pressure monitor with a stethoscope.
- A green card: "ALREADY KNOW YOUR CHOLESTEROL NUMBER? Take our Heart Age test >"
- A blue card: "DR. KNOW OZ's YOUR 5 THE LIFESAVING NUMBERS YOU NEED TO KNOW" with a list:
 - BLOOD PRESSURE
 - WAIST SIZE
 - WEIGHT
 - CHOLESTEROL
 - FASTING BLOOD SUGAR

Your Fecal Number - Useful?

- *Currently, used in screening only - number tells if colonoscopy recommended. Just using the number for this seems a waste of data.*
- *Number tells how like, or unlike, you are to your peers by gender and age.*
- *Number tells your future risk if below cut-off fecal Hb concentration used in screening for referral for colonoscopy,*
- *Number may tell how often screening is needed,*
- *Number may be usefully included in scoring systems.*

Which FIT is "Best"?

- *There are a number of analytical systems available.*
- *It is difficult for users to make objective choices.*
- *Many papers on FIT compare one gFOBt with one only FIT.*
- *Some evaluations use "spiked" feces, which do not truly mimic human materials.*
- *Certain evaluations compare results with more than one analytical system but use different participant cohorts.*
- *Ideally, two (or more) systems are evaluated simultaneously using fresh specimens collected from one feces passed by real participants in a structured screening program.*

Data - Taiwan Jan 2010 - Oct 2011

Analytical System	Number	Positive (%)	Cancer (%)	Polyps (%)
HM-JACK	703507	9.01	0.27	2.96
OC Sensor	964100	5.63	0.14	1.28
Total	1667607	7.06	0.19	1.99

*Analyses: over 120 certified hospitals and commercial laboratories.
 Methods: different buffer, antibodies, etc.
 f-Hb cut-off: concentrations as recommended by manufacturers.
 Different populations?*

NO "BEST" can be recommended at present.

***Uses of FIT in Clinical Settings
Other than Screening***

- paediatrics
- patients with real difficulties in bowel visualisation
- evaluation of mucosal healing in UC
- follow-up of known colorectal disease (surveillance)
- familial CRC investigation and follow-up
- and for the SYMPTOMATIC – although the dogma is that FOBT are of no use in assessment of the symptomatic.

Fraser CG. Ann Clin Biochem 2012;49:518-26.

Finally

I hope that, now, you:

- appreciate the need for screening for colorectal neoplasia and the role of fecal tests,
- are able to list the advantages and disadvantages of guaiac-based FOBT, FIT, and quantitation of fecal hemoglobin,
- recognize that fecal hemoglobin concentration is related to both disease severity and risk,
- appreciate that there are still controversies about best use of FIT in screening programmes, and
- are able to contemplate the potential roles of FIT other than in screening.
