

Detection of Bowel Cancer: FIT for Purpose?

Callum G Fraser

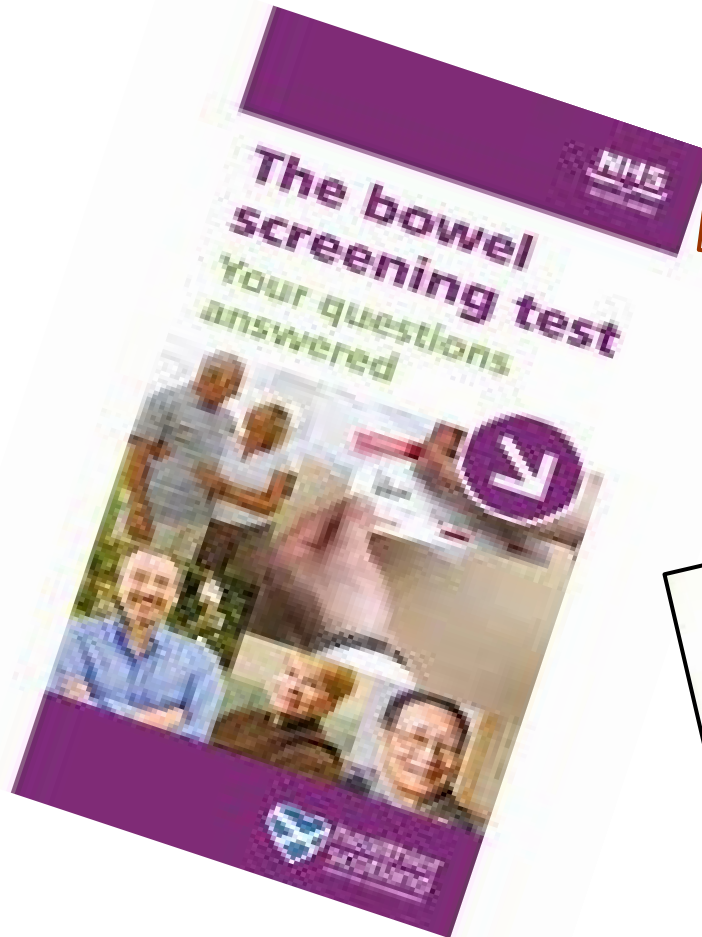
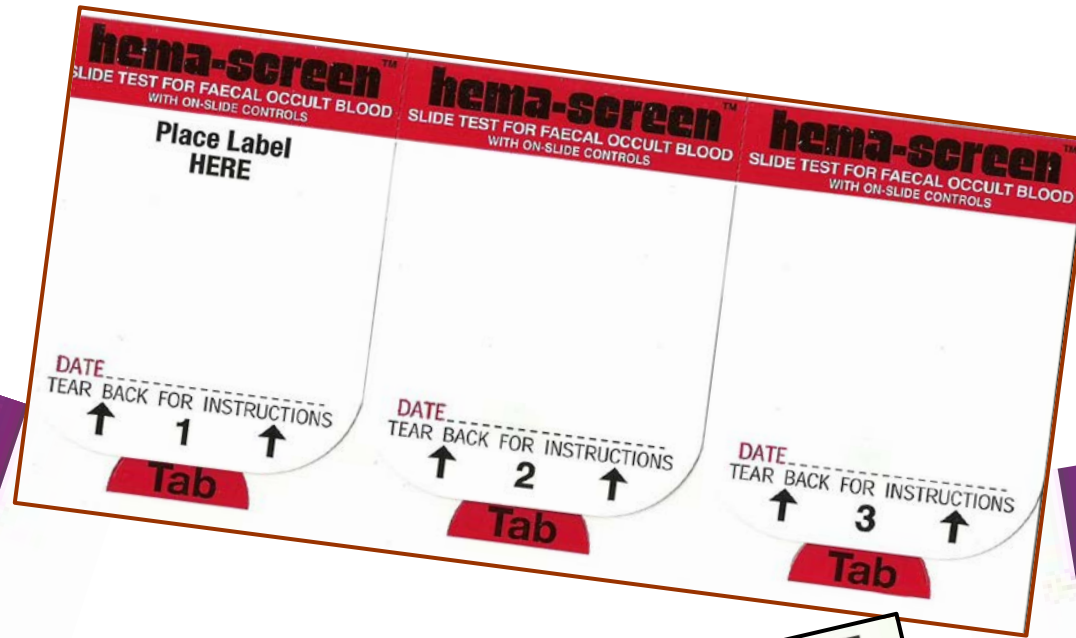
Centre for Research into Cancer Prevention and Screening

University of Dundee Scotland



Bowel Screening:

Scottish Bowel Screening Programme



Scottish Bowel Screening Programme Statistics.

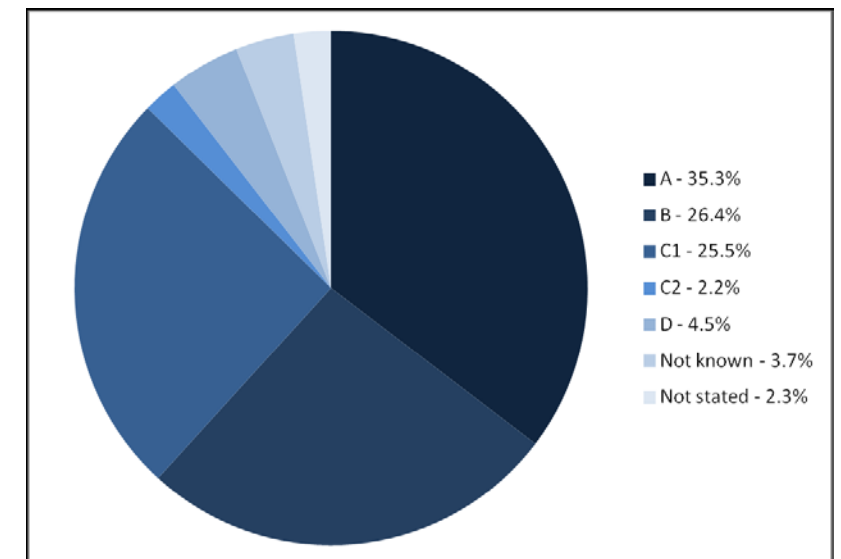
For invitations - 1 November 2012 and 31 October 2014.
Publication date – 04 August 2015.



Key points:

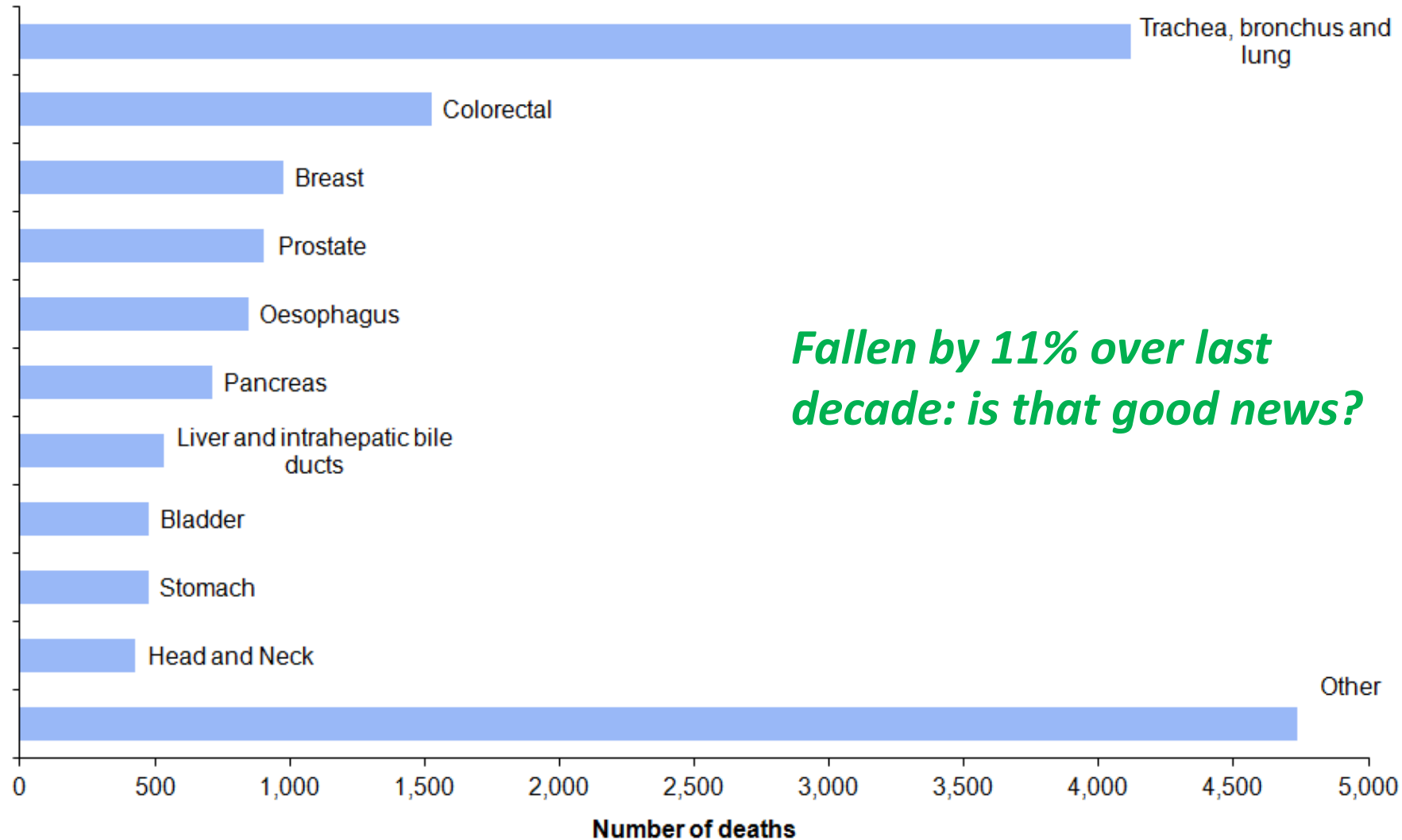
- For the two-year period: the number of participants exceeded **one million** for the first time.
- Uptake was 57.6%, **an increase of 1.5%**. Uptake **for females was 60.3%** and **for males was 54.7%**.
- Just over 2% received a positive test result. Of those, 6.9% had a bowel cancer.
- 61.7% of screen detected cancers were diagnosed at the **earliest two stages**.
- **Uptake was lower in areas of higher deprivation.**

The earlier a cancer is detected the greater the chances are of successful treatment



Cancer Mortality in Scotland (2014).

Publication date – 17 November 2015.



Fallen by 11% over last decade: is that good news?

Cancer Incidence Projections for Scotland 2023-2027.

Publication date -18 August 2015.



*The number of new cases of cancer is **predicted to rise by 33%** between 2008-2012 and 2023-2027, mainly as a result of the population growing older.*


	<i>Actual 2008-12</i>	<i>Projected 2023-27</i>	<i>Percentage change</i>
<i>Bladder</i>	8,905	11,366	27.6
<i>Brain</i>	2,145	2,590	20.8
<i>Breast (female)</i>	22,421	28,579	27.5
<i>Cervix</i>	1,594	2,225	39.6
<i>Colorectal</i>	19,833	28,298	42.7
<i>Uterus</i>	3,235	5,016	55.1
<i>Kidney</i>	4,672	8,030	71.9
<i>Lung</i>	25,475	30,648	20.3

Screening for Colorectal Cancer - for Individuals *WITHOUT* Symptoms.


- **Colonoscopy.**
- **Flexible sigmoidoscopy.**
- **CT colonography.**
- **DNA analysis of faeces and/or blood.**
- **Faecal and blood tests – bewildering variety.**
- **Tests for the presence of hemoglobin in faeces – markers of bleeding into gut.**

Screening Tests

Carbohydrate antigen 19-9 (CA 19-9)




Septin 9 methylated DNA is a sensitive and specific blood test for colorectal cancer





ScheBo® • Tumor M2-PK™ EDTA Plasma Test

carcinoembryonic antigen (CEA)




Epigenomics Licenses Septin 9 Diagnostics



Methylated vimentin

p53 gene
K-ras /KRAS gene
APC gene



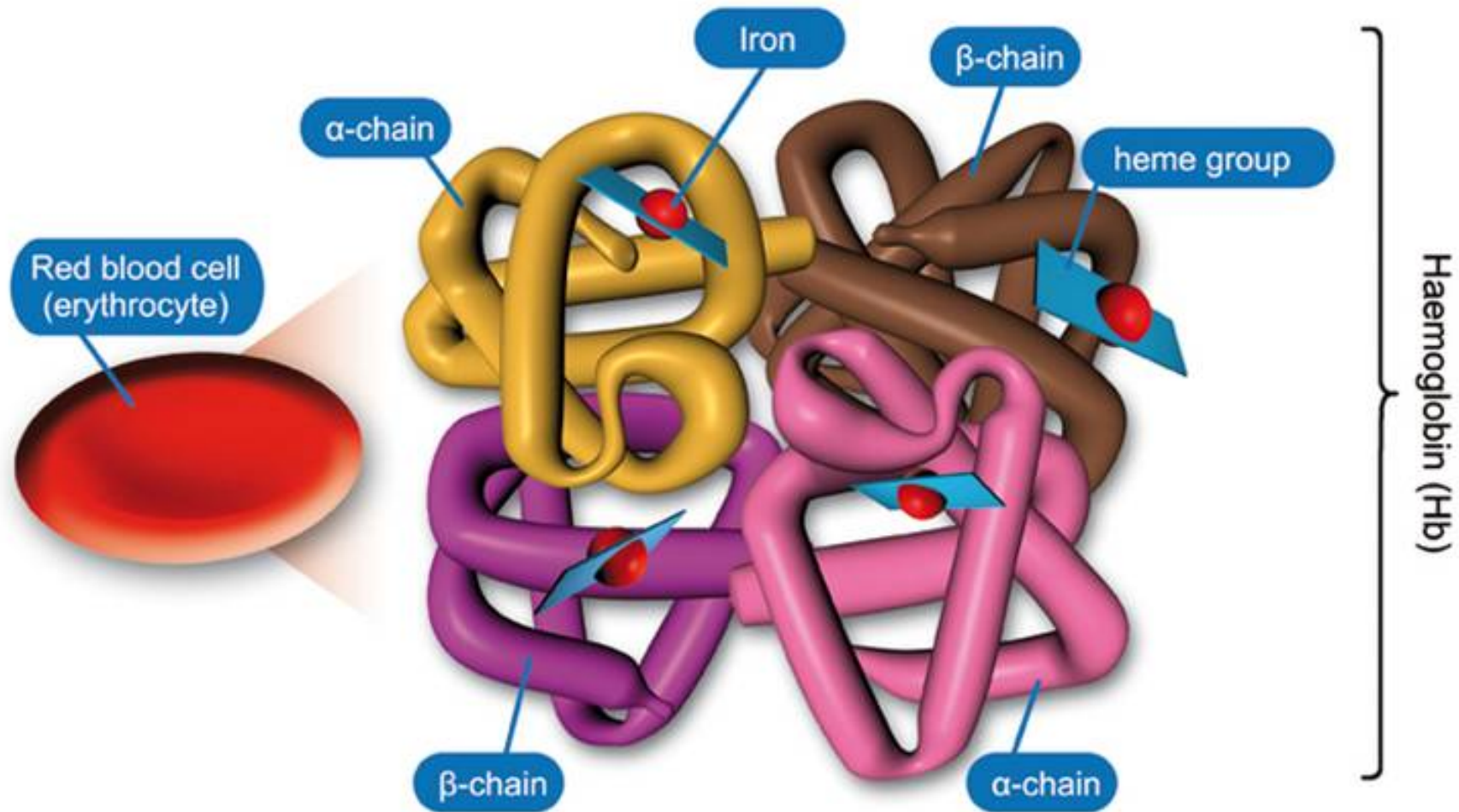
Proteins (M2-PK)

Epidermal growth factor receptor (EGFR)

THE SEPTIN 9 TEST
Blood-based colorectal cancer screening is available for your patients who are unwilling or unable to have a colonoscopy

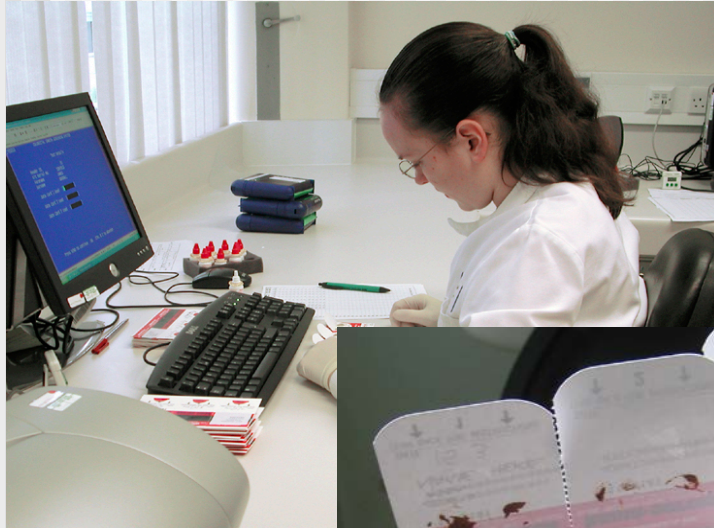
Structure of haemoglobin

haem + globin



Each erythrocyte (RBC) contains ~270 million haemoglobin molecules

Guaiac-based FOBT - gFOBT



A number of gFOBT available - based on pseudoperoxidase activity of haem reacting with peroxide in the developer





Minnesota



Nottingham



Funen

1990s - Large Randomised Controlled Trials Using *gFOBT*



16% reduction in mortality

gFOBT Adopted Widely for Screening.

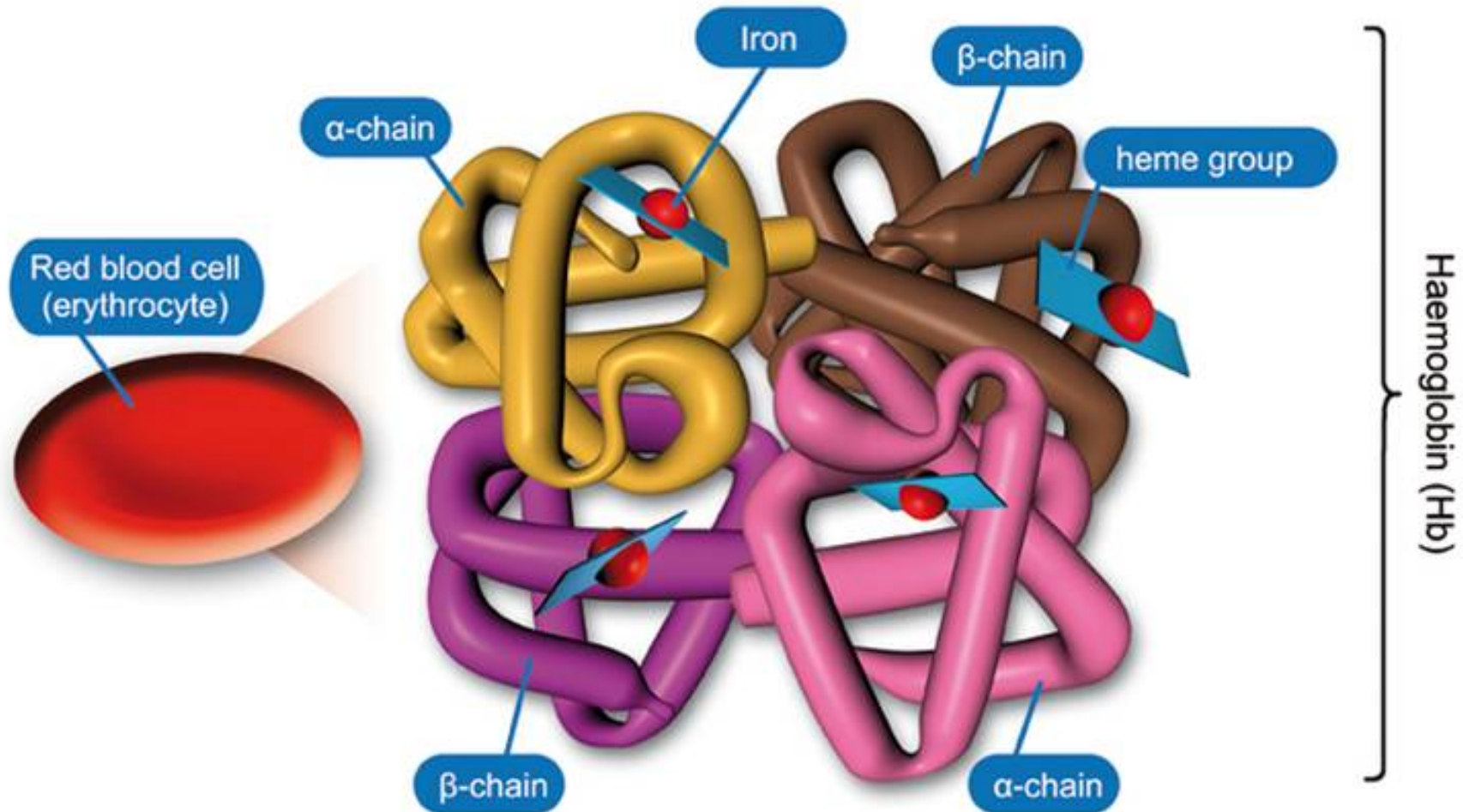
Some Advantages *BUT* Many Disadvantages:

- ***Multiple samples required.***
- ***False positive results (positive test result but normal colonoscopy) and false negative results (shown by interval cancers – especially in women).***
- ***Potential for interference from meat and certain vegetables.***
- ***Detect bleeding from stomach, small and large intestine.***
- ***Not easy to interpret colours – reader variation. Cannot be “automated”.***
- ***Cut-off concentration set by manufacturer – so positivity - and colonoscopy demand – and clinical outcomes - set by manufacturer.***
- ***Now considered “obsolete” by many experts and opinion leaders.***



Structure of haemoglobin

haem + globin



Each erythrocyte (RBC) contains ~270 million haemoglobin molecules

Faecal Immunochemical Tests (FIT) for Haemoglobin.

- *Detect human haemoglobin with antibodies to globin.*
- *One sample only – generally easier to collect - with user friendly, hygienic specimen collection devices.*
- *No dietary interferences.*
- *More specific for lower GI lesions.*
- *Generally more analytically sensitive than gFOBT.*
- *Can be automated and give an estimate of faecal haemoglobin.*
- *Now advocated in many publications and recommended in most modern guidelines – for population screening – THE best non-invasive investigation.*

THE FIT (R)EVOLUTION IS HERE!

Haemoglobin Concentration is Related to Disease Severity



Normal → *Low risk adenoma* → *High risk adenoma* → *Cancer*

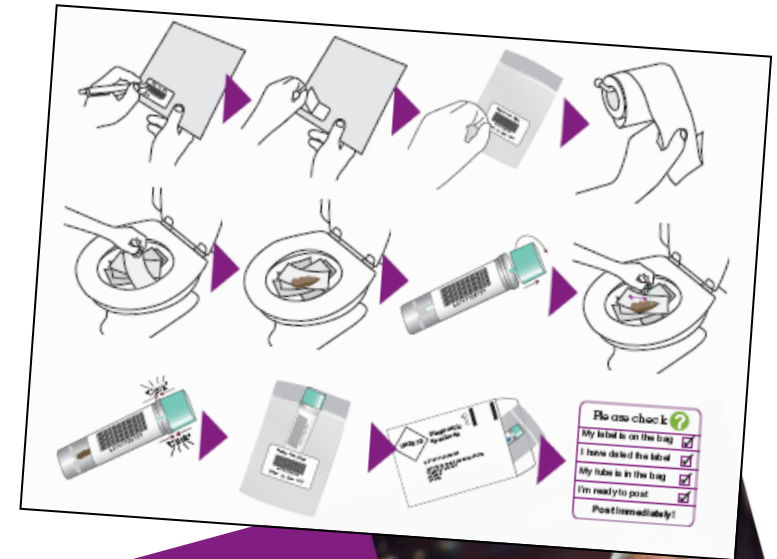
Faecal Haemoglobin



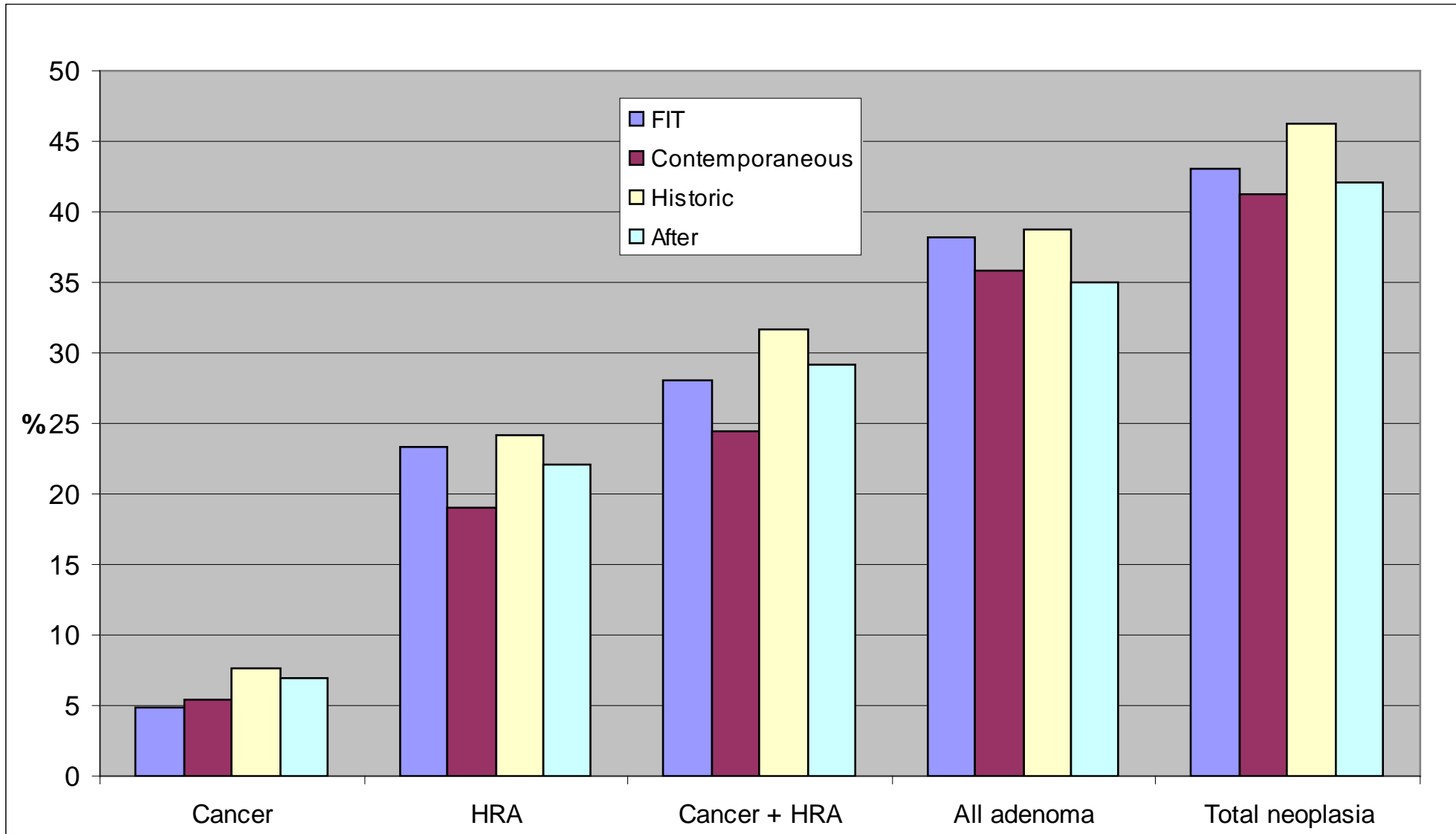
Digby J, et al. J Clin Path 2013; 66:415-41.

Design of the FIT as a First-Line Test Evaluation.

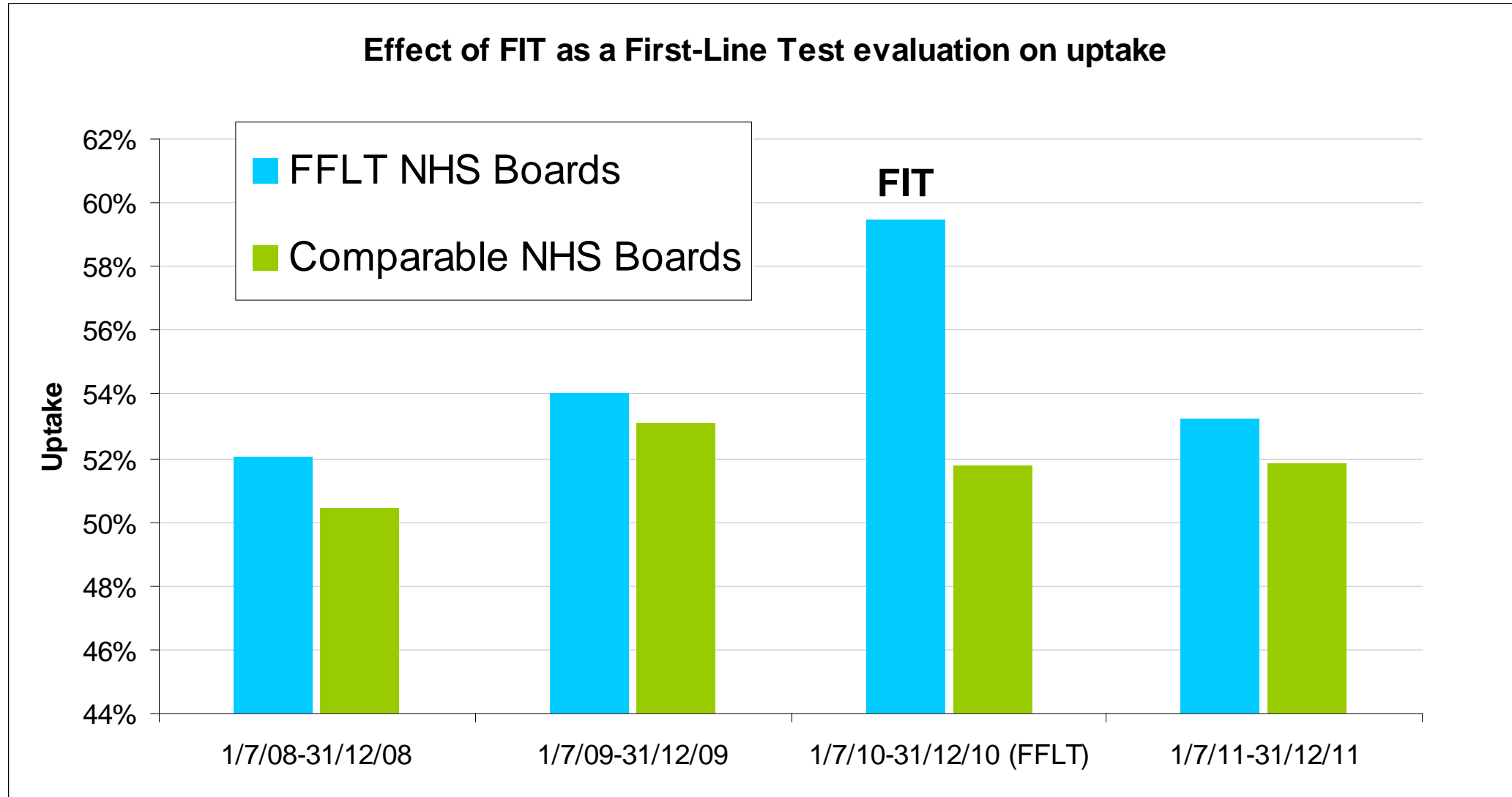
- **Invitation period July 2010 – January 2011**
- **NHS Ayrshire & Arran and NHS Tayside**
- **70,000 sequential invitations**
- **One sample**
- **Cut off 400 ng Hb/ml buffer (80 µg Hb/g faeces)**
- **Comparisons done with NHS Forth Valley and NHS Fife**



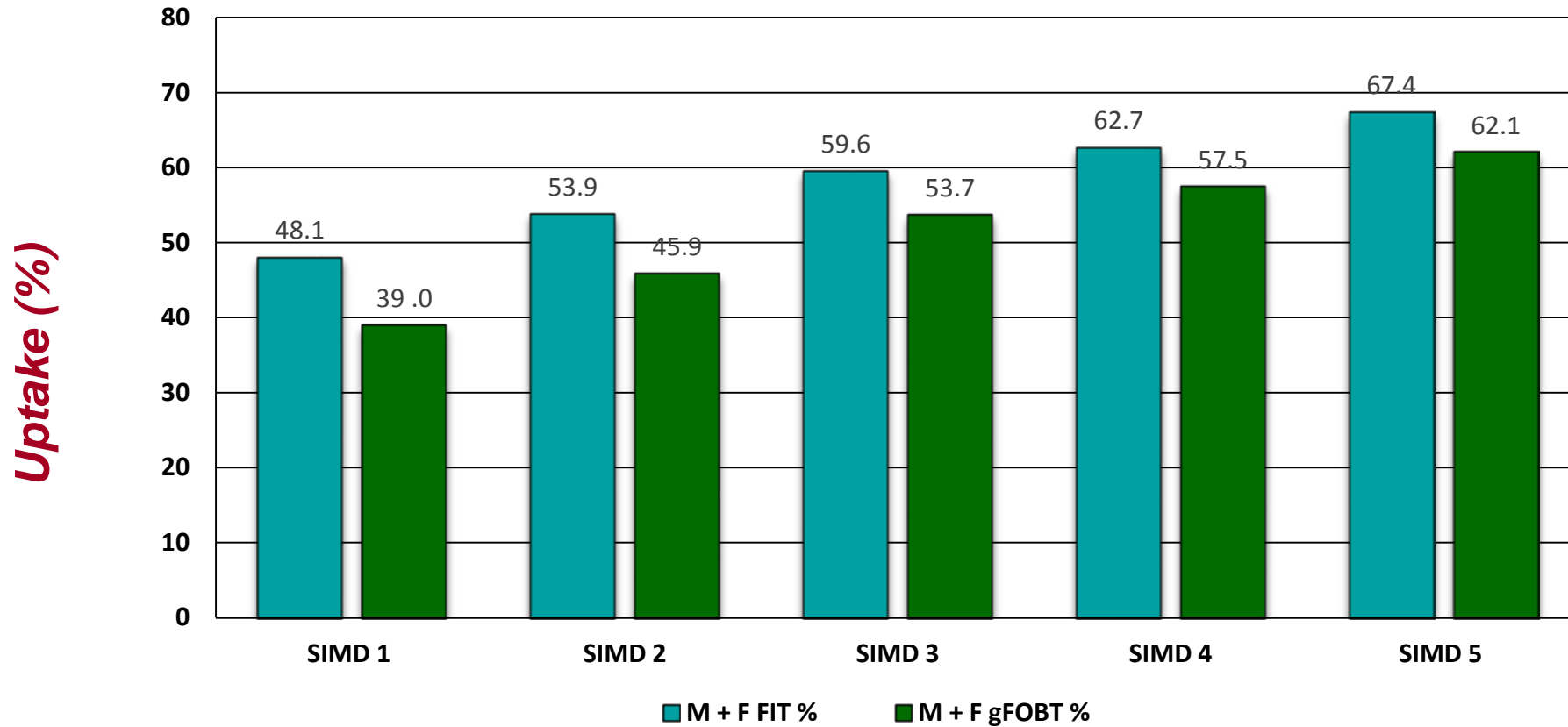
Outcomes – Clinical Comparison (PPV = true/total positives).



Uptake in FIT as a First-Line Test NHS Boards and Comparable NHS Boards.



Outcome – Increased Uptake in More Deprived Groups.



Scottish Index of Multiple Deprivation Quintile

Evaluation Outcomes.

- **Introduction of FIT as a first-line test in Scotland supported by:**
 - **clinical outcomes at least as good as current screening strategies using gFOBT as the initial test and**
 - **increased uptake, easy of use – few calls to Helpline, and practicability of the FIT analysis.**
- **Cost-Benefit Analysis and Business Case for FIT prepared.**
- **Change now approved by Scottish Government.**

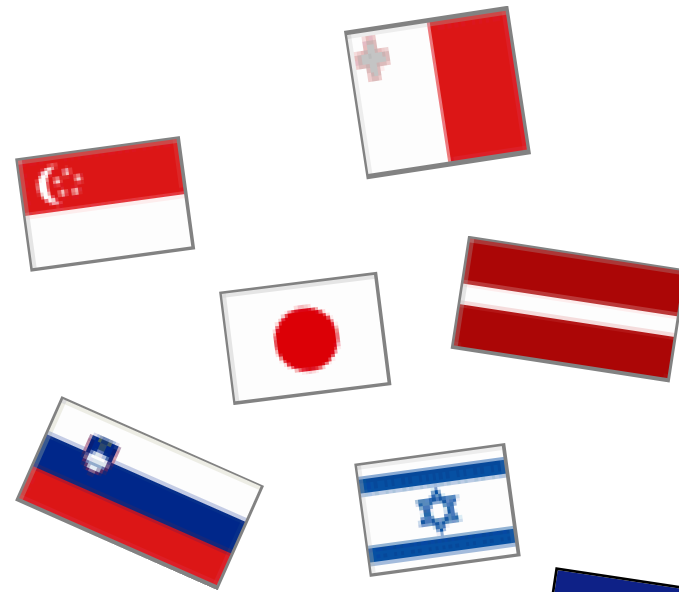
Get Fit





- in good company.

Faecal Immunochemical Test (FIT)



European guidelines for quality assurance in colorectal cancer screening and diagnosis. Chapter 4. Faecal occult blood testing.
Endoscopy 2012;44 (S 03):SE65-SE87

Issues with FIT – Cut-off f-Hb Used Determines Outcomes.



Normal → *Low risk adenoma* → *High risk adenoma* → *Cancer*

Faecal Haemoglobin



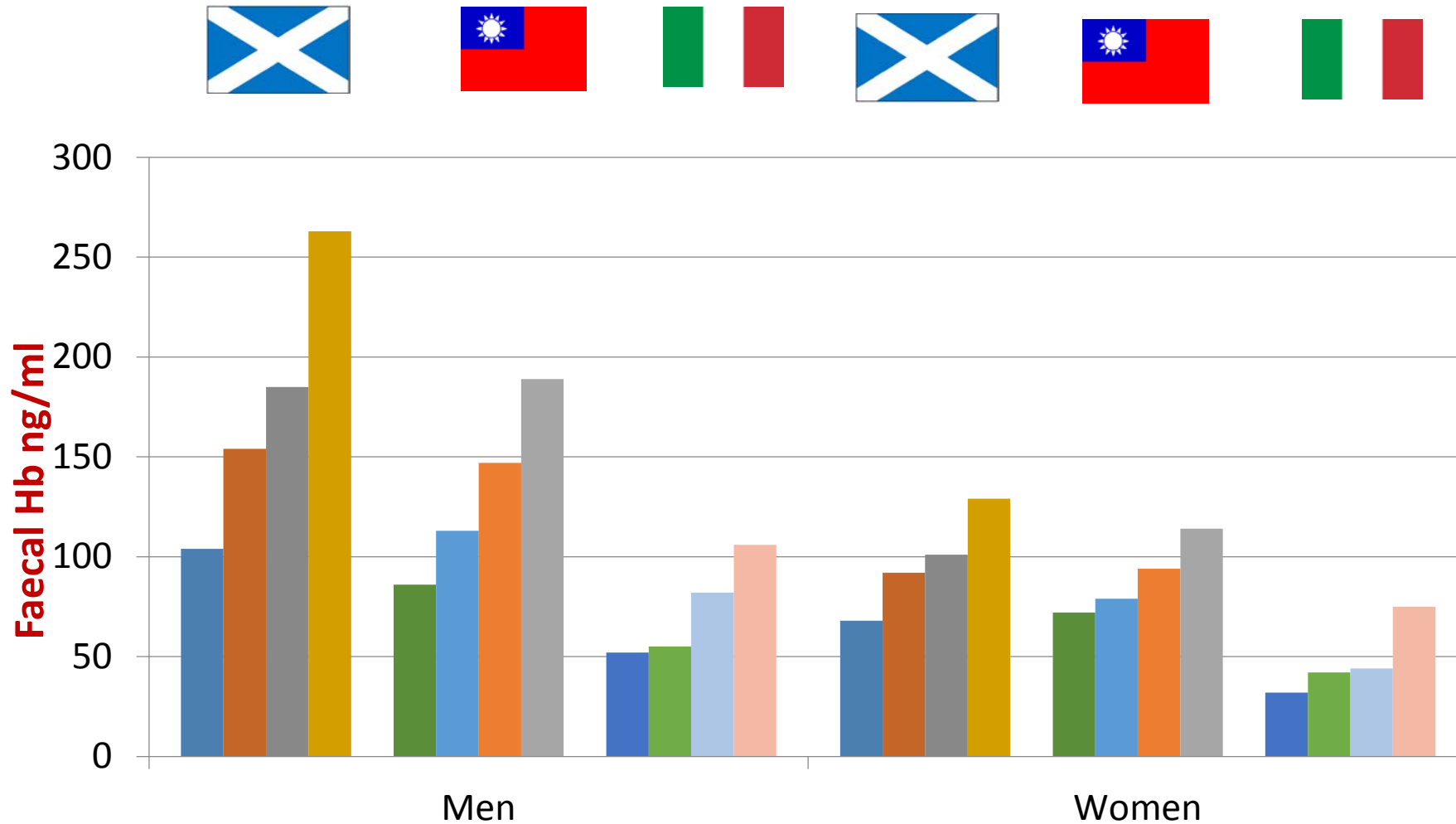
Digby J, et al. J Clin Path 2013; 66:415-41.

Outcomes (%) with FIT at Different Cut-off Concentrations.

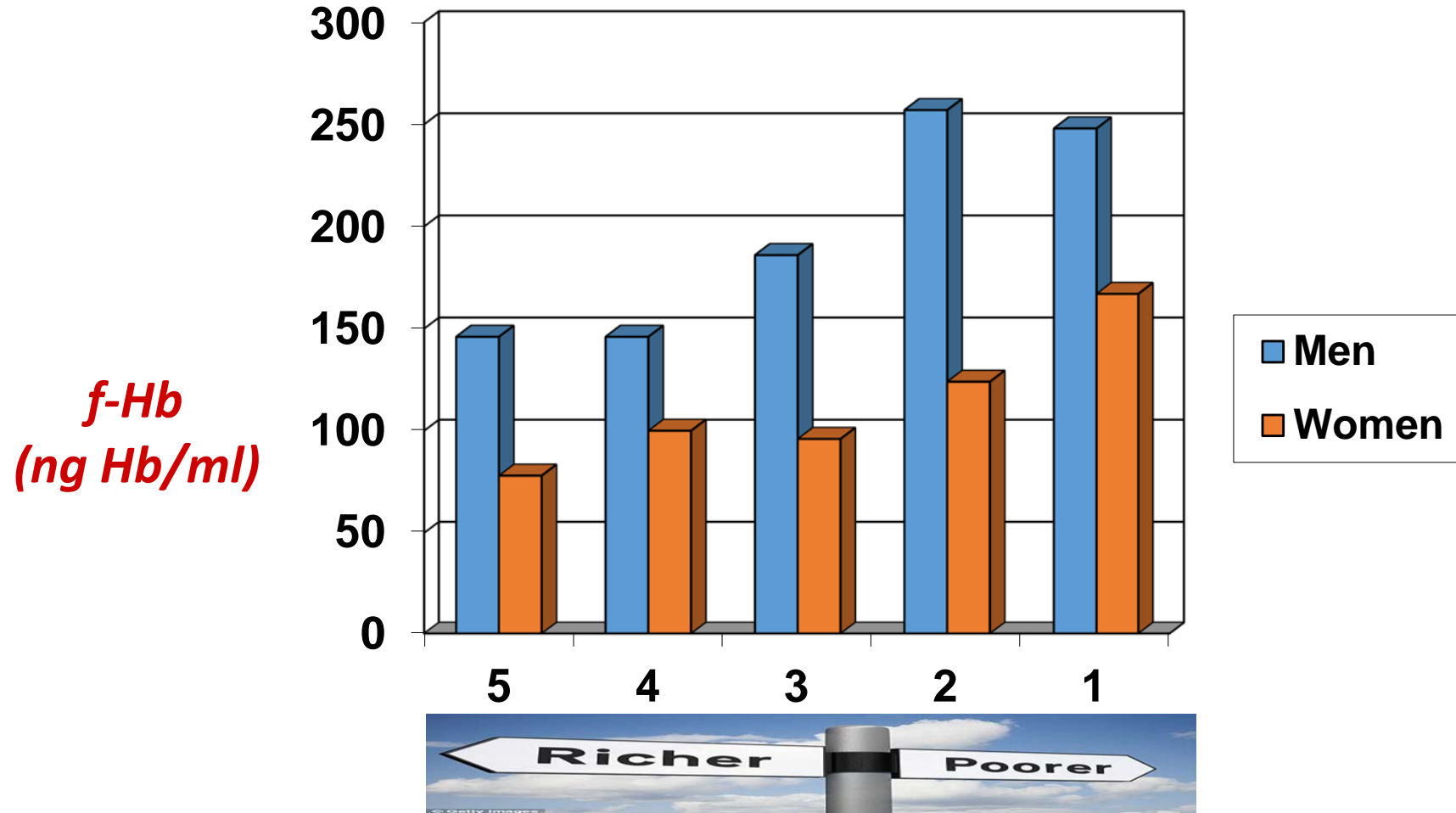
$\mu\text{g Hb/g faeces}$	Positivity	Detection Rate for AN	PPV	Specificity
FIT 10	8.1	3.2	42	95.5
FIT 15	5.7	2.7	49	97.2
FIT 20	4.8	2.5	53	97.8
FIT 25	4.1	2.3	57	98,2
FIT 30	4.0	2.3	60	98.4
FIT 35	3.6	2.2	63	98.7
FIT 40	3.5	2.1	62	98.8

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

Issue - f-Hb Varies by Age and Sex - Three Countries - 50-69 years.



Issue – f-Hb Varies with Deprivation - 50-74 years.

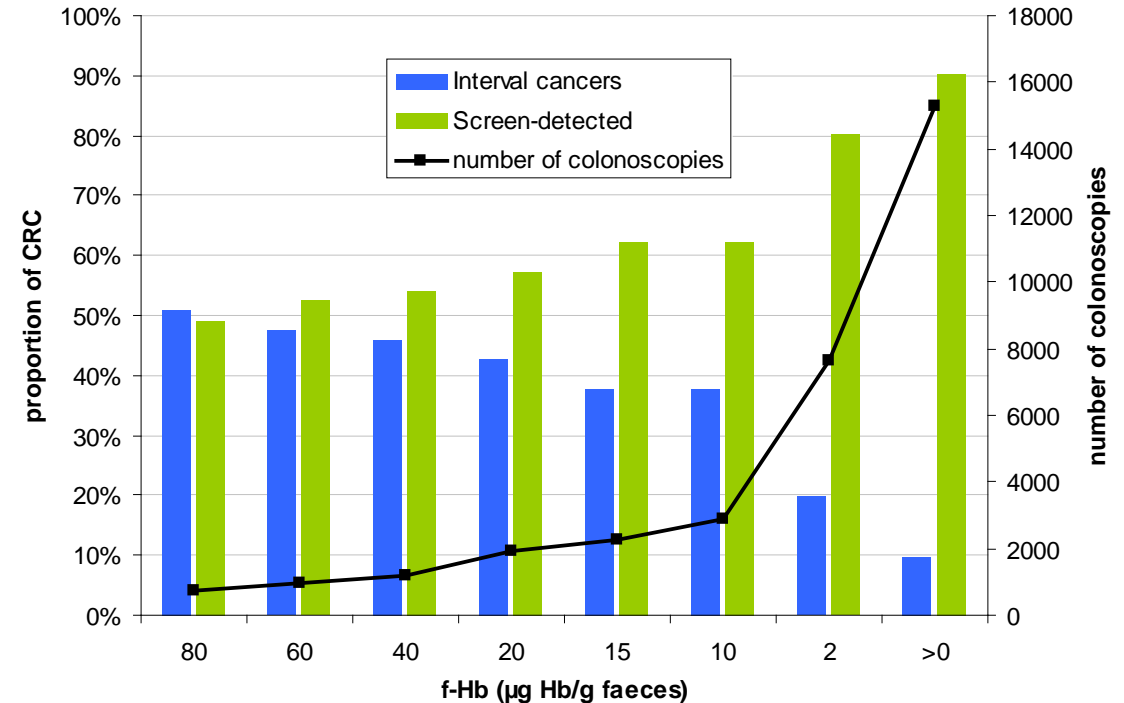


Scottish Index of Multiple Deprivation quintile

Digby J, et al. J Med Screen 2014;21:95-7.

Issue - Interval Cancers with High Cut-off f-Hb.

- **Defined as a “colorectal cancer diagnosed after a negative screening test result and before the date of the next recommended examination”.**
- **Interval cancer rate with FFLT was similar to gFOBT at 50.8%.**
 - **48.4% in men, 53.3% in women.**
- **Those with faecal Hb concentration 60.0-79.9 $\mu\text{g/g}$ more likely to have an IC compared with those with lower f-Hb.**



Digby J, et al. J Med Screen 2016; in press.

FIT are IT for Screening - But - Future Challenges.

- ***Use **ONE** only OR **different** f-Hb cut-off concentrations for men and women and/or for young and old?***
- ***Report “risk” – from f-Hb alone?***
- ***Use more sophisticated data analysis - add age and sex - or add other factors such as deprivation - to create a “score”?***
- ***Treat people as individuals? Keep records of individual’s faecal haemoglobin concentration and consider changes over time?***

Some difficult to implement - more research needed.

How Is Colorectal Disease Found – Particularly Neoplasia?

Investigating symptoms (primary care)

Colonoscopy

Screening for colorectal cancer

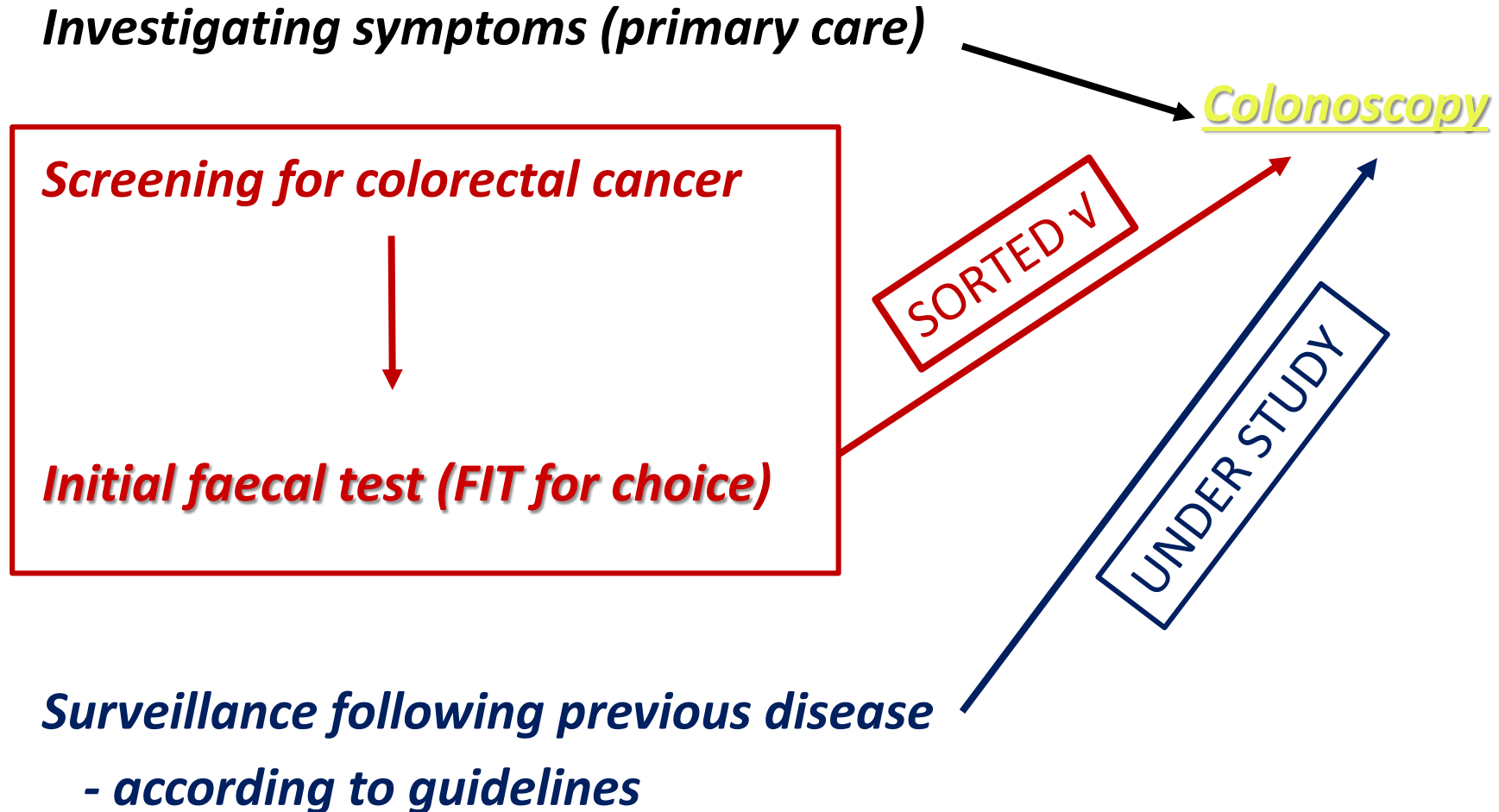


Initial faecal test (FIT for choice)

SORTED ✓

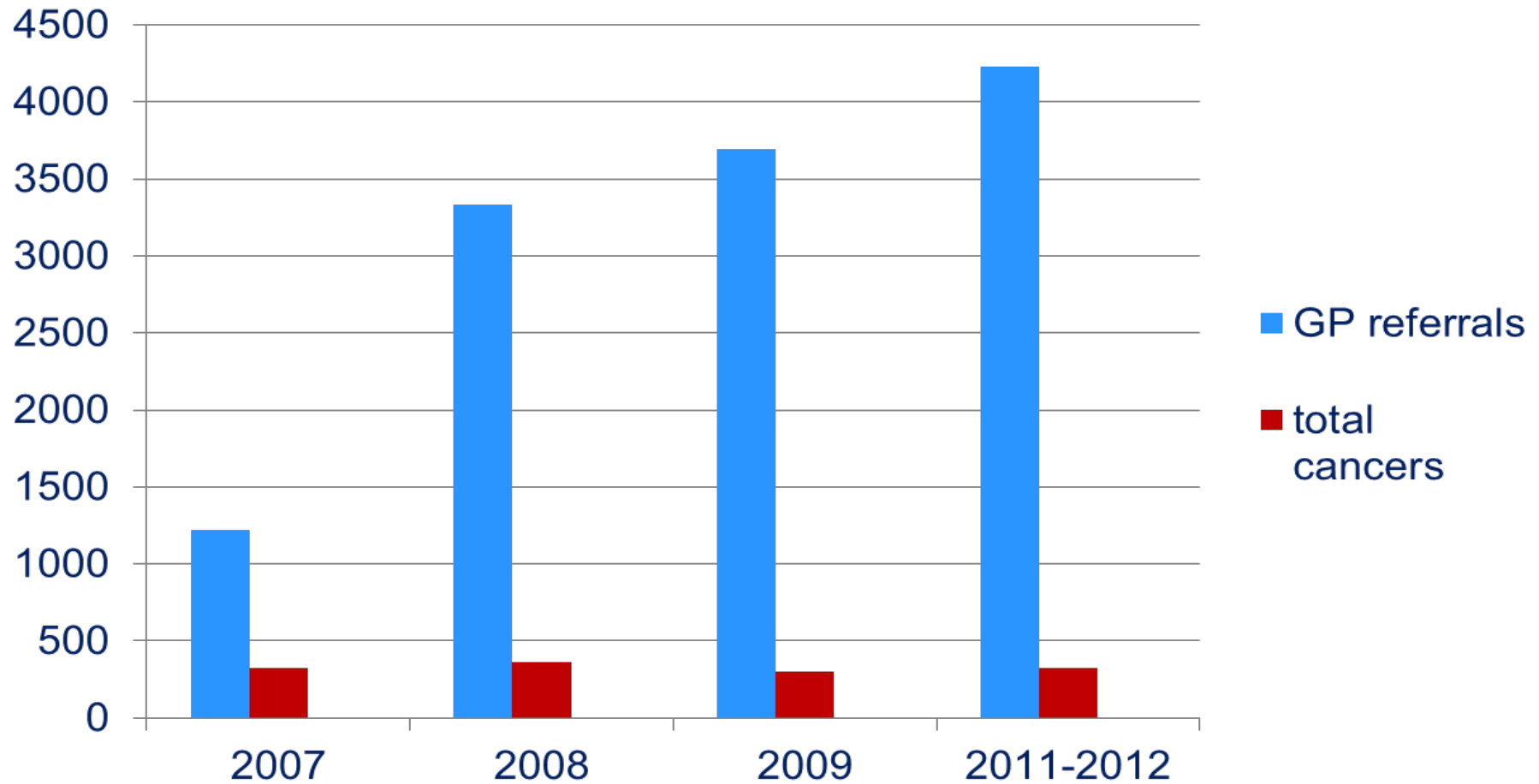
UNDER STUDY

*Surveillance following previous disease
- according to guidelines*



Colorectal Pathway Referrals – Primary Care – NHS Tayside.

The Colonoscopy “Crisis”



Assessment of the Symptomatic – Patients Presenting with Lower Abdominal Symptoms in Primary Care.

McDonald PJ, et al. Colorectal Dis 2013;15:e151-9. 280 patients

FITS 10 µg Hb/g faeces: CRC sensitivity - 100% NPV for SCD - 88.1%

Mowat C, et al. Gut – Online. 570 patients.

**3 of 28 CRC missed
– all women**

FITS+ 10 µg Hb/g faeces: CRC sensitivity - 89.3% NPV for SCD - 94.4%

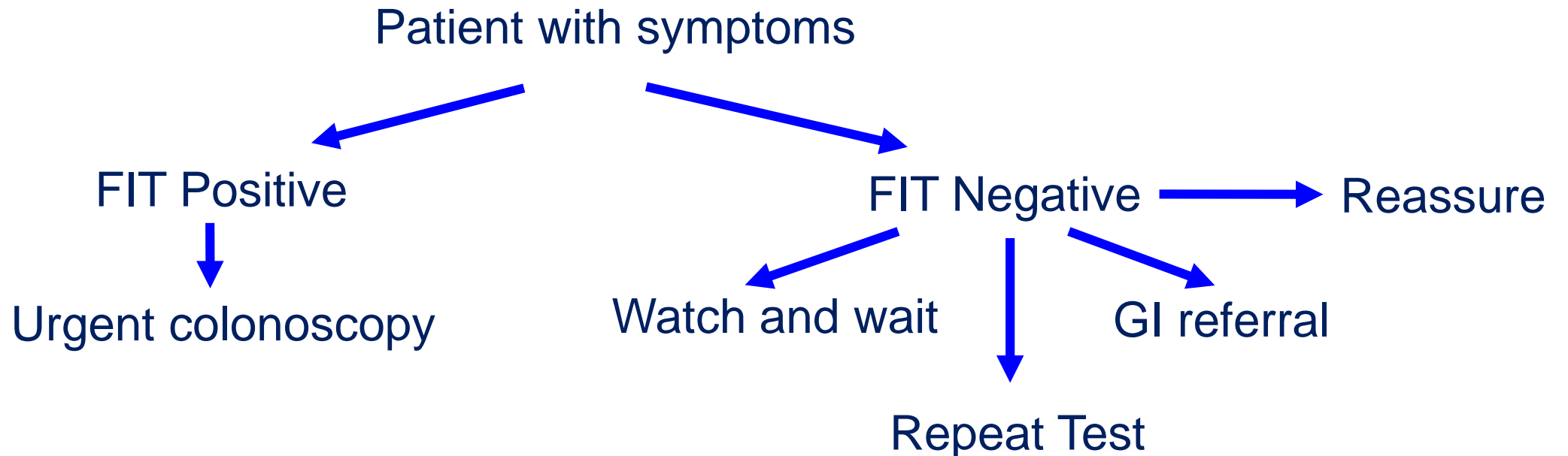
Godber IG, et al. Clin Chem Lab Med – Online. 484 patients.

FITS2 10 µg Hb/g faeces: CRC sensitivity - 100% NPV for SCD - 96.2%



The Future of Assessing Patients Presenting in Primary Care?

- *No test is perfect - but FIT can be used to **rule in** cancer in symptomatic patients and, perhaps more importantly, **rule out** significant colorectal disease.*
- *No. of referrals for urgent colonoscopy could be cut by up to half.*
- *Some – smaller adenomas and cases of IBD - would be missed.*



Detection of Colorectal Disease – The New f-Hb Paradigm.



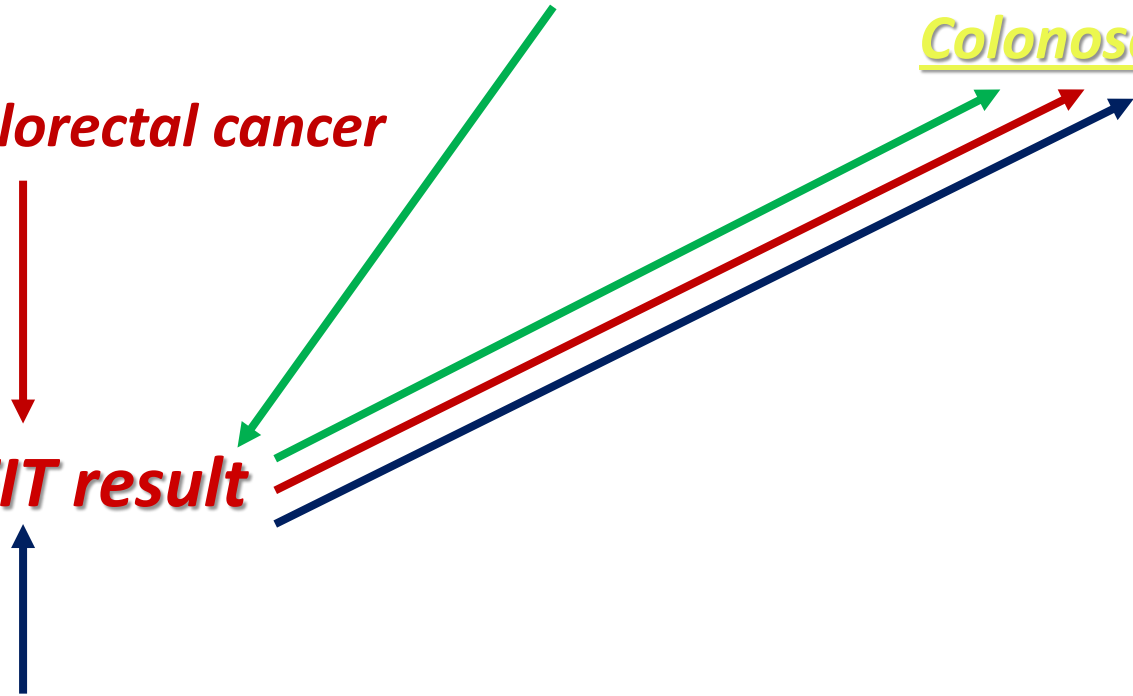
Investigating symptoms (primary care)

Screening for colorectal cancer

Initial FIT result

*Surveillance following previous disease
- according to guidelines*

Colonoscopy

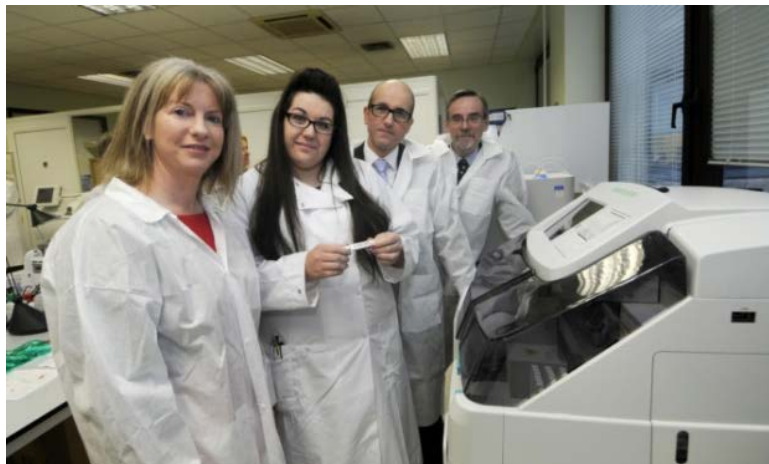


Current work on f-Hb in Diagnosis in Scotland.

- Use different f-Hb cut-off for men and women and/or young and old?
- Assess “risk” – from f-Hb alone – or with age and sex – or plus other factors?



**The *FAST* Score –
*F*aecal Hb, *A*ge and *S*ex *T*est**



**Chief Scientist Office - £300K.
Study to investigate bowel cancer ‘risk score’.
Study aimed at ultimately assisting GP.**

Overall Conclusions – FIT are FIT for Purpose!

- **Screening using FIT has many advantages over gFOBT but needs better use of quantitative f-Hb estimates to ensure equality across age and sex.**
- **FIT provide a very good test to *rule in* CRC and *rule out* significant colorectal disease in patients with lower abdominal symptoms. Use of FIT in primary care could direct scarce endoscopy resources to those who would benefit most.**
- **Research is needed how best to apply the quality numerical estimates of f-Hb that can be made with FIT – in screening AND in diagnosis – and other settings.**

With many thanks to:

Robert JC Steele, Jayne Digby, Paula J McDonald, Craig Mowat, Francis A Carey, Judith A Strachan, Annie S Anderson, Josep-Maria Auge, Stefano Rapi and Tiziana Rubeca, Ian M Godber and Louise Todd, Sam Chen and Tony Chen, and more!