



**3rd EUROPEAN COLORECTAL CANCER DAYS:**  
**BRNO 2014 – PREVENTION AND SCREENING**  
25–26 April 2014, Brno, Czech Republic



# Why FIT (*Faecal Immunochemical Test*) is the best biomarker for CRC screening



**Prof. Stephen Halloran**

- Royal Surrey County Hospital
- NHS Cancer Screening Programme
- University of Surrey

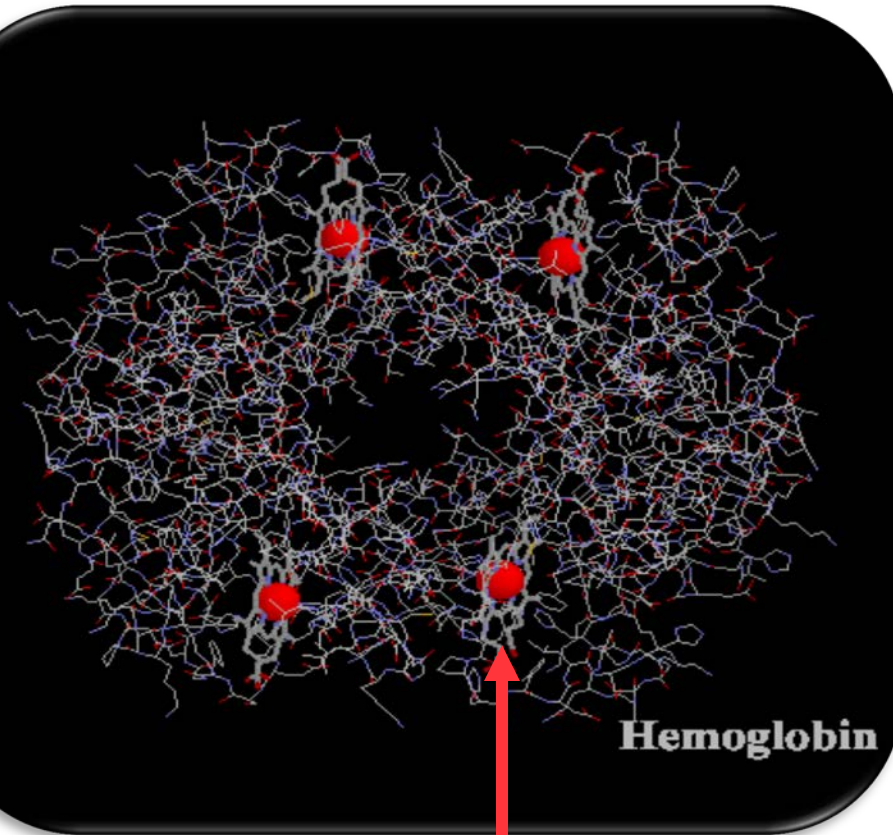
gFOBt

# Guaiacum Officinale - Lignum Vitae





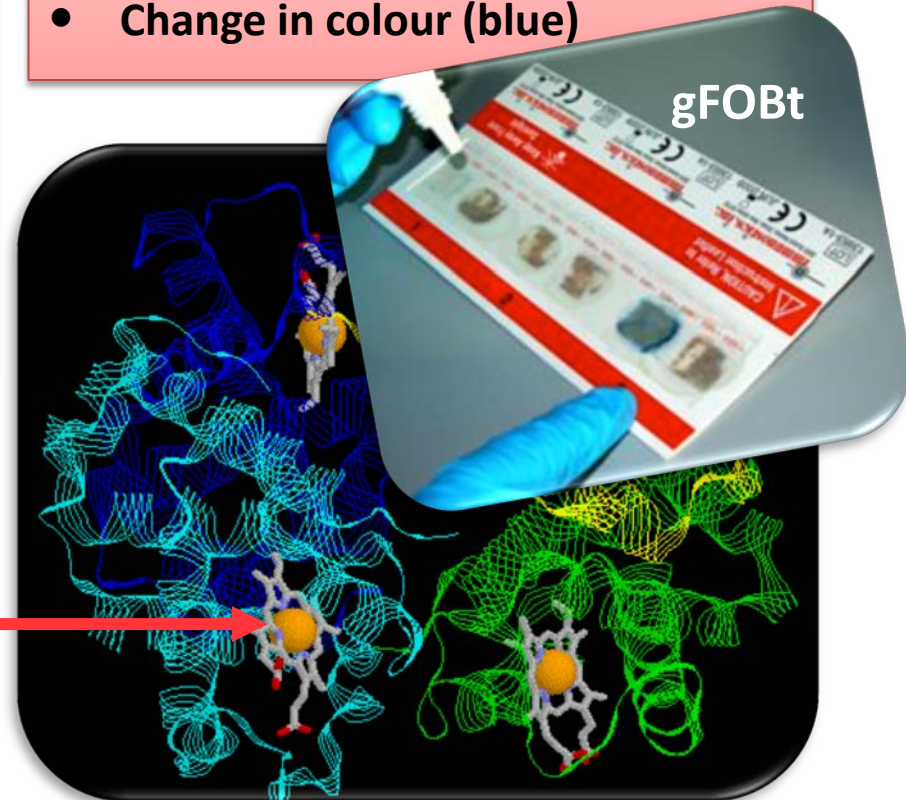
# Guaiac Faecal Occult Blood Test



Haem

## Haemoglobin - Haem

- Haem (containing iron)
- Release of oxygen from  $\text{H}_2\text{O}_2$
- Oxidise a dye (**guaiac**)
- Change in colour (blue)



BBC

NHS Bowel Cancer Screening Southern Programme

NHS

Bowel Cancer Screening  
Southern Programme

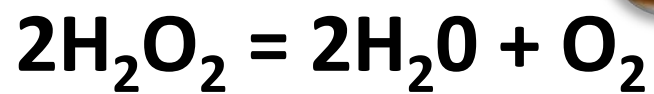


Professor Stephen Halloran  
Southern Screening Hub Director

goes the theory  
**bang**







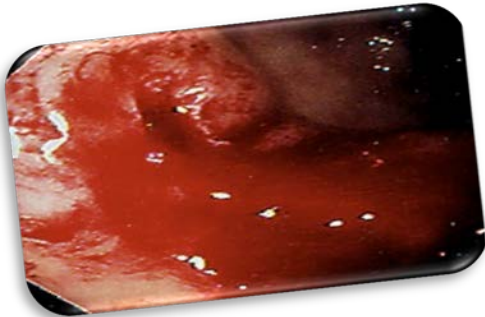




# Will they do the test???

They'll never do it!

It's just too gross!





# 1990's Large Randomised Controlled Trials Using **FOBT**



The NEW ENGLAND  
JOURNAL of MEDICINE

**Sept. 19, 2013 369;12 Nishihara et al**  
30 year update - Minnesota RCT

## Annual gFOBT

- After 13 years - 33% reduction of CRC mortality
- After 30 years - 32%

## Biennial gFOBT

- Both 13 and 30 years about 22%

## Message – polypectomy effective in reducing CRC

US (Minnesota)

## UK (Nottingham)

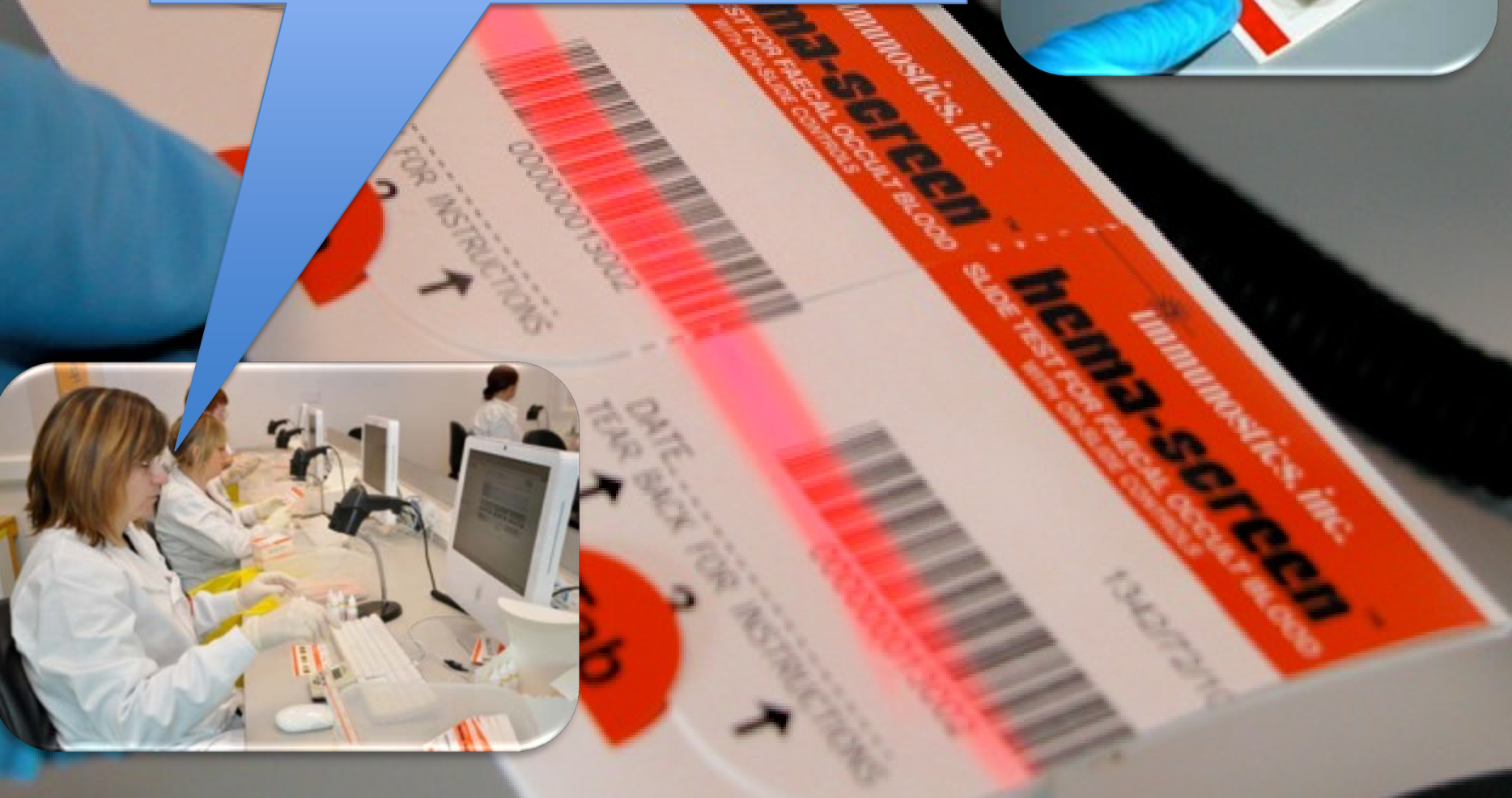
# Denmark (*Funen*)

# France (*Dijon*)

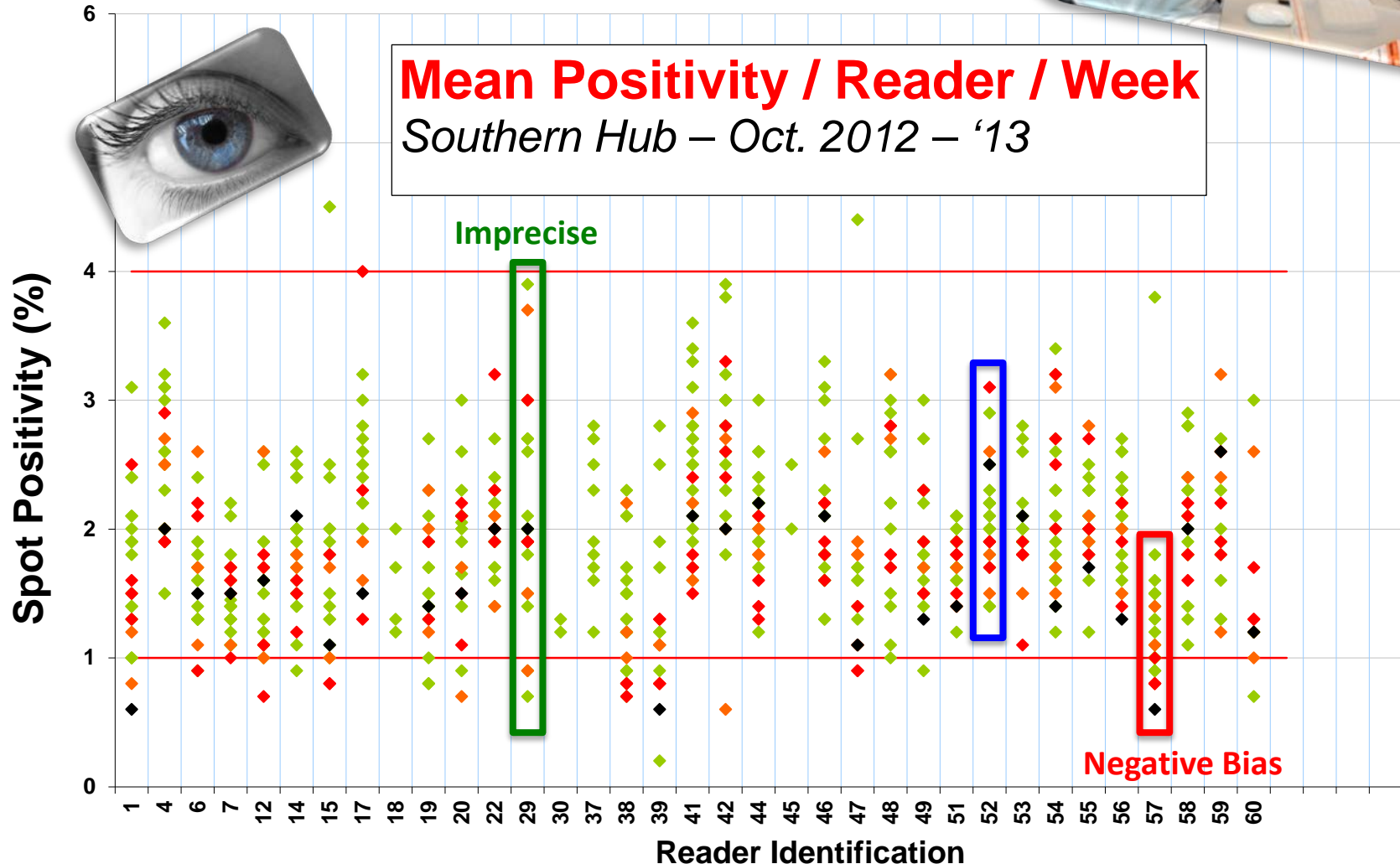


## Strengths

- Cheap test
- Mailing – simple & cheap
- Records patient ID and date
- 3 Opportunities to find blood

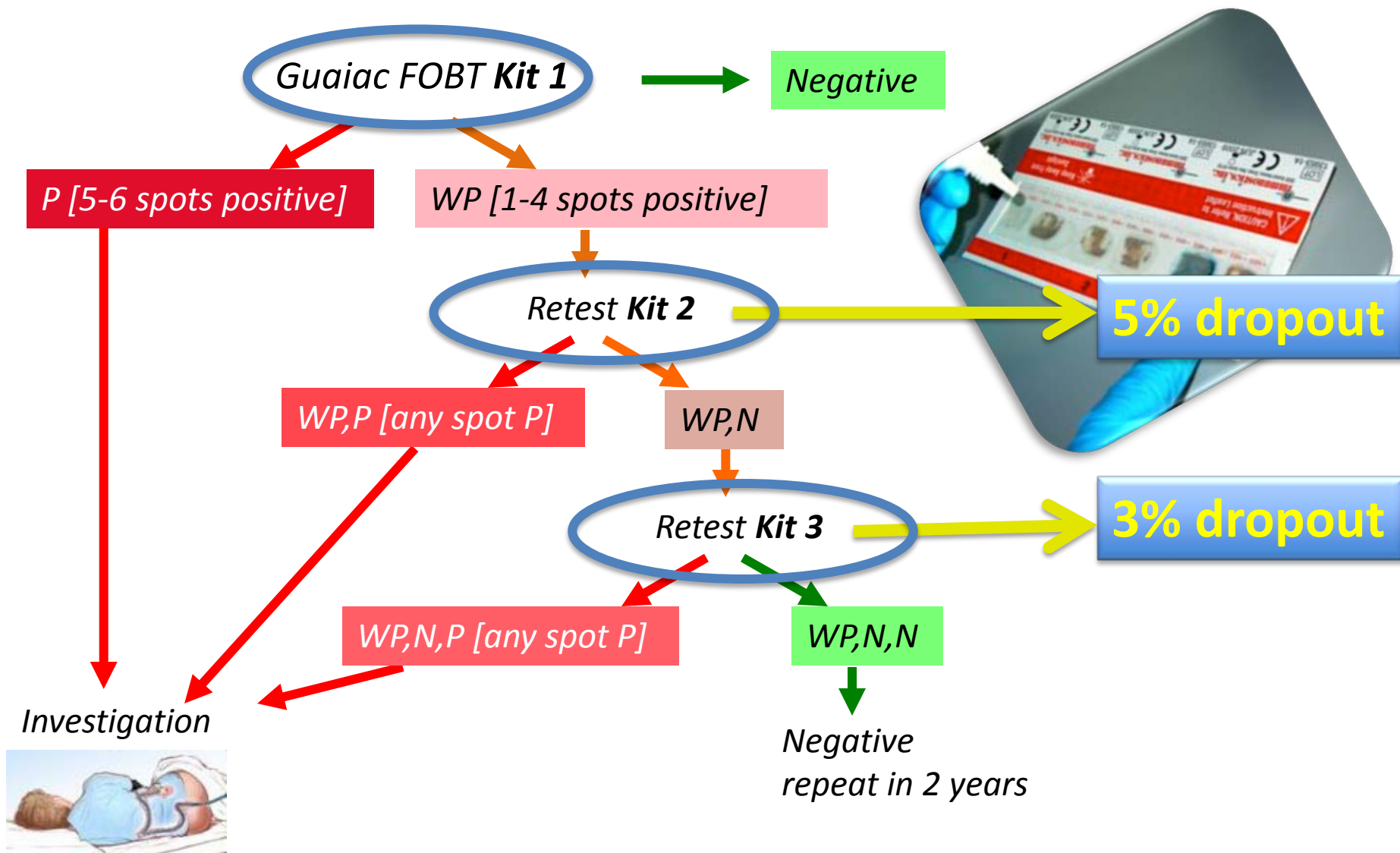


# gFOBT - A significant analytical challenge!





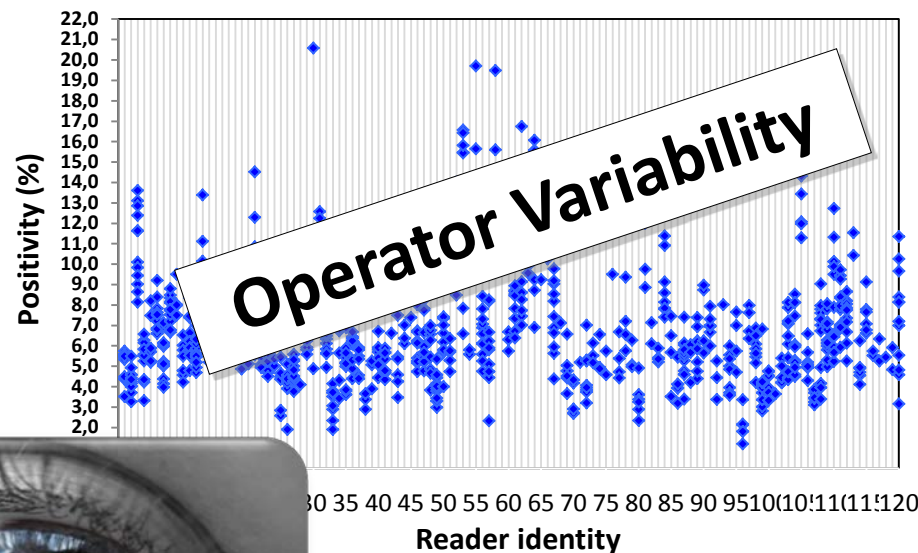
# The English '*three –kit algorithm*'



# Why we need a *Better Test for Haemoglobin*



**No Automation**



**Can't adjust positivity**

**3 samples,  
3 kits, 3 letters,  
3 analysis**



# Colorectal Cancer

## *The Ideal Population Marker*



- **Detect all CRC & ‘pre-cancers’**
  - Early stage Dukes A & B cancers
  - **Advanced adenomas**
  - No false positives

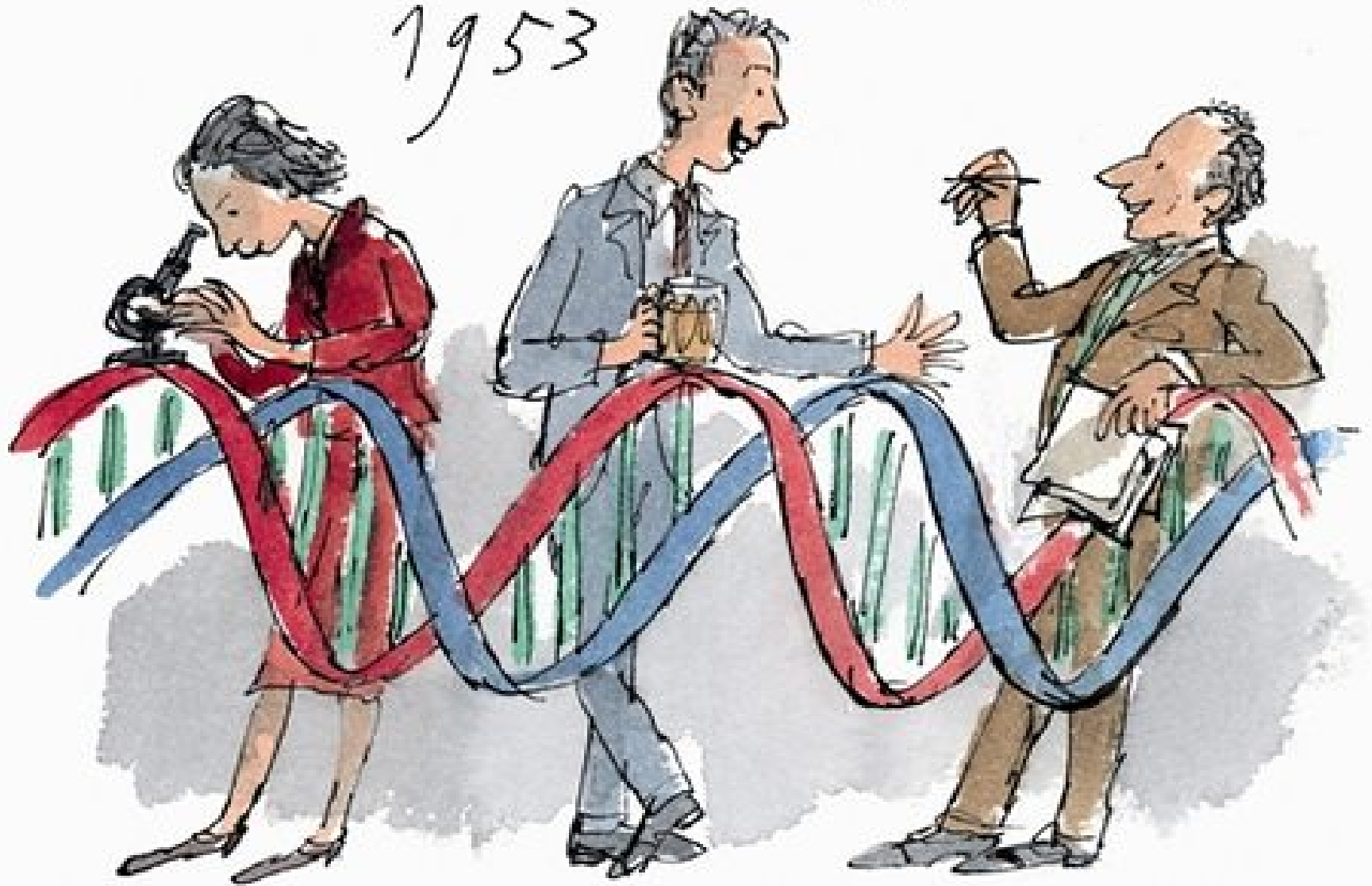
- **Simple Sampling**
  - Home
  - GP Clinic



- **Analysis Easy & Reliable**
- **No interference**
  - Sample stable
  - Temperature
  - Light
  - Diet or drugs
  - Other diseases
- **Affordable!**

# DNA: Franklin, Crick & Watson

1953





Carbohydrate antigen  
19-9 (CA 19-9)

# Method of Screening

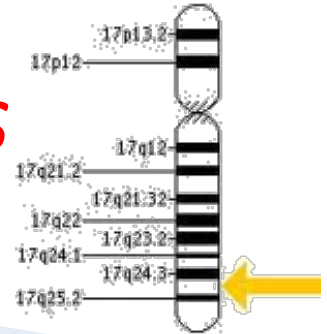
## Non-Invasive Investigations



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

carcinoembryonic antigen (CEA)

ScheBo® • Tumor M2-PK™ EDTA Plasma Test



Epigenomics Licenses Septin 9  
Diagnostics



Methylated vimentin

**Calprotectin**  
Intestinal Inflammation Assay



**THE SEPTIN 9 TEST**

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

p53 gene  
K-ras /KRAS gene  
APC gene

Proteins (M2-PK

Epidermal growth factor receptor (EGFR)

# Method of Screening

## *Non-Invasive Investigations*

### FDA Advisers Back Exact Sciences Colon Cancer Test

WASHINGTON March 27, 2014 (AP)

Exact Sciences Moves Closer to Preventing the No. 2 Cancer Killer



#### Multi-target Stool DNA & FOBT test

- FOBT (FIT)
- Methylated BMP3 & NDRG4
- Mutant KRAS & B-Actin



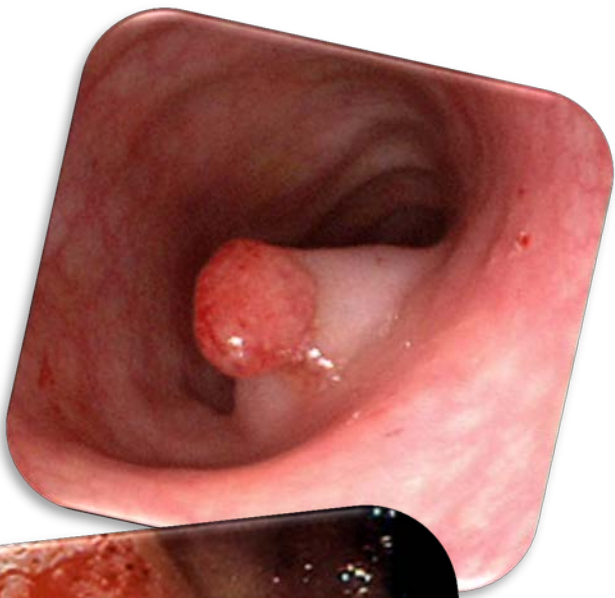
The NEW ENGLAND  
JOURNAL of MEDICINE

#### Multitarget Stool DNA Testing for Colorectal-Cancer Screening

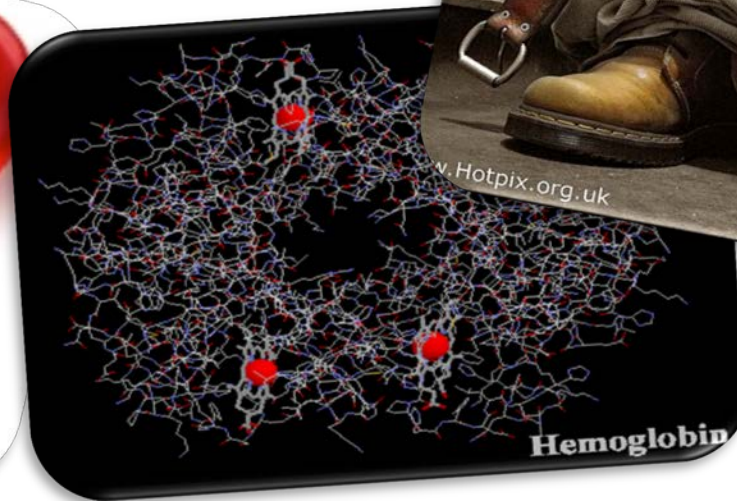
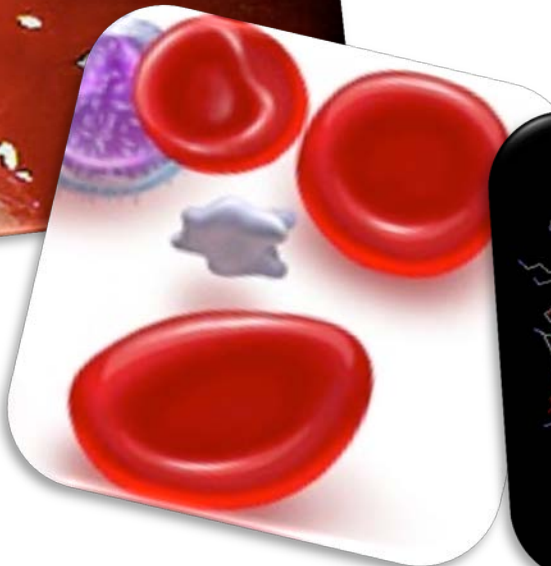
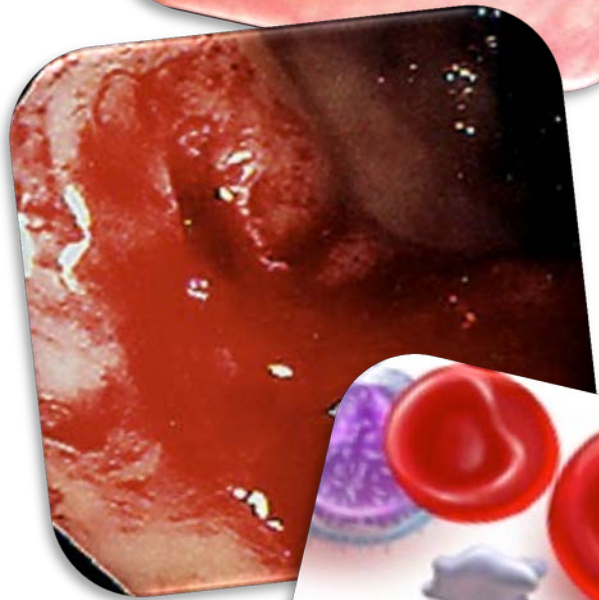
Thomas F. Imperiale, M.D., David F. Ransohoff, M.D., Steven H. Itzkowitz, M.D., Theodore R. Levin, M.D., Philip Lavin, Ph.D., Graham P. Lidgard, Ph.D., David A. Ahlquist, M.D., and Barry M. Berger, M.D.

March 19, 2014 | DOI: 10.1056/NEJMoa1311194

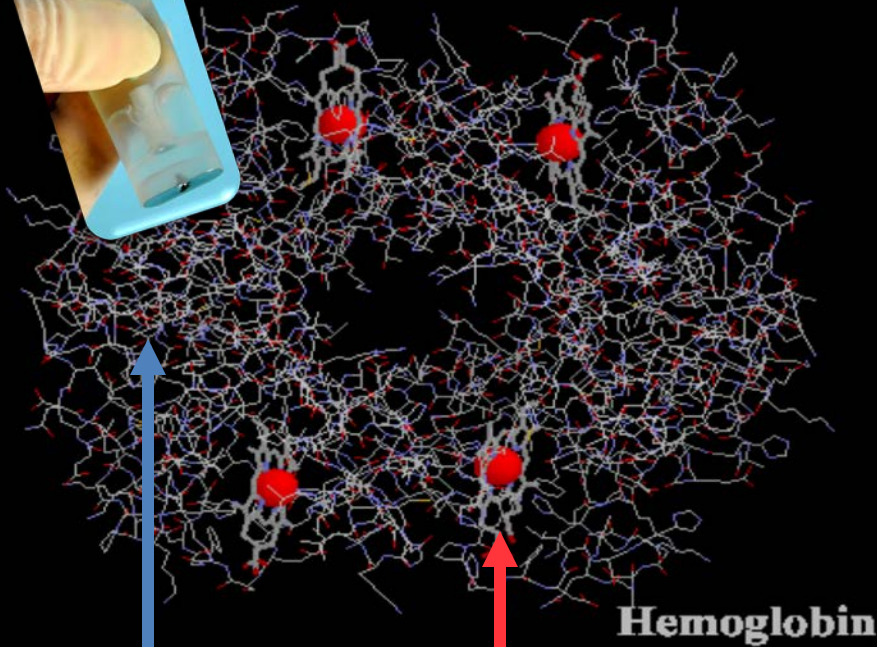
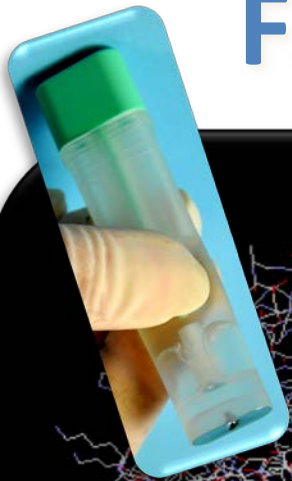




**Blood in faeces  
...still the best marker!**



# Faecal Immunochemical Test



Hemoglobin

Haem

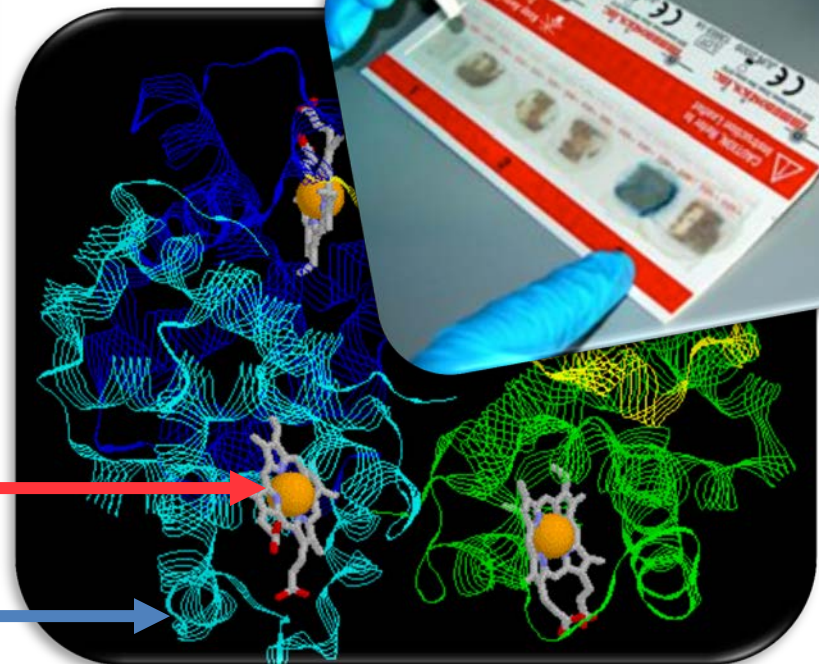
Globin

## Haemoglobin - Globin

- Antibody recognition of the tertiary structure produced by the folding of the amino acid chain in the globin protein.



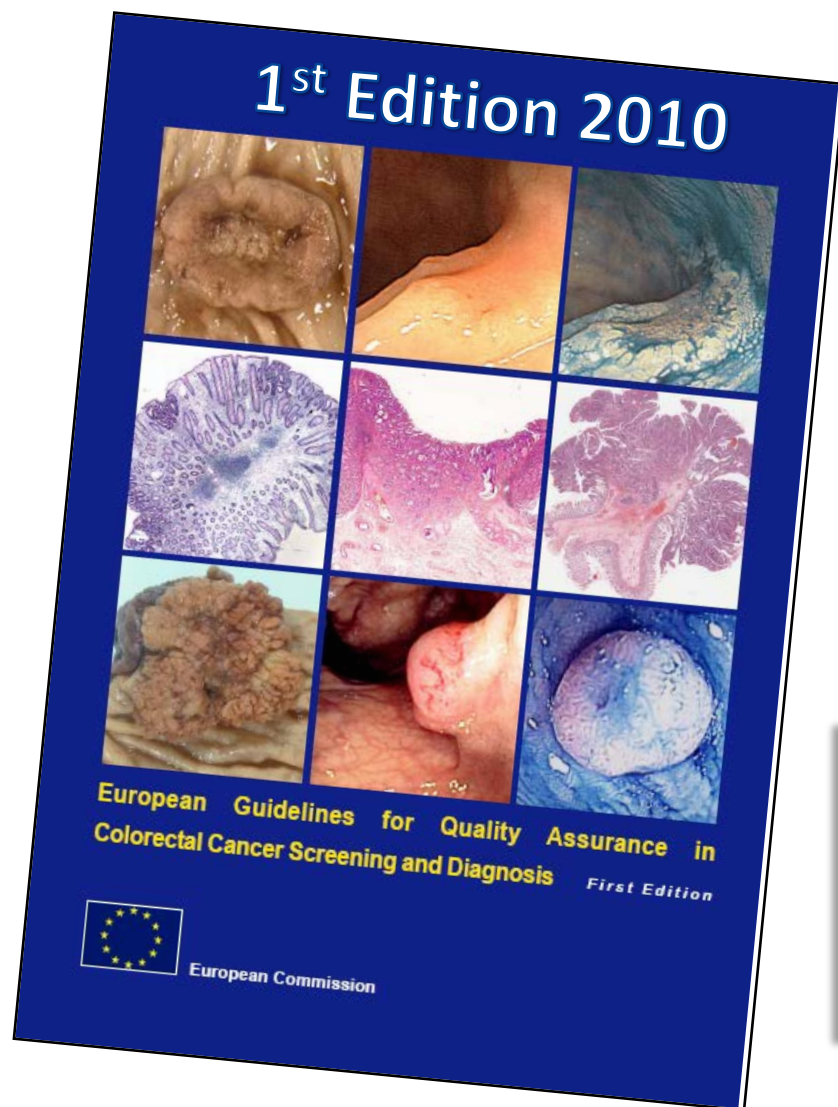
gFOBt







# EU Guidelines for Quality Assurance in Colorectal Cancer Screening



## Faecal Immunochemical Test



European guidelines for quality assurance in colorectal cancer screening and diagnosis. Chapter 4. Faecal occult blood testing.

**Endoscopy 2012; 44 (S 03):SE65-SE87**

# FIT Measures Concentration of Haemoglobin

Outcome	Mean FIT Conc. ug Hb /g faeces	Positives at 20 ug /g Cut-off
Normal	10 (1-20)	6.9%
All Adenoma	14 (4-25)	9.3%
Adv. Adenoma	81 (37-125)	34.5%
Cancer	170 (55-252)	84.6%

Endoscopic Classification	Mean FIT Conc. ug Hb /g faeces	+ve at 20 ug /g Cut-off
<b>Histology</b>		
LGD	27	14.1%
HGD	197	50.0%
<b>Size</b>		
< 10 mm	12	9.0%
≥ 10 mm	99	36.4%
<b>Number</b>		
< 3 adenoma	14	10.1%
≥ 3 adenoma	65	26.7%

## OC-SENSA MICRO

Dong Il Park, MD<sup>1</sup>, Seungho Ryu, MD<sup>2</sup>, Young-Ho Kim, MD<sup>3</sup>, Suck-Ho Lee, MD<sup>4</sup>, Chang Kyun Lee, MD<sup>4</sup>, Chang Soo Eun, MD<sup>5</sup> and Dong Soo Han, MD<sup>5</sup>



# Study relating OC Sensor FIT concentration and outcome at colonoscopy

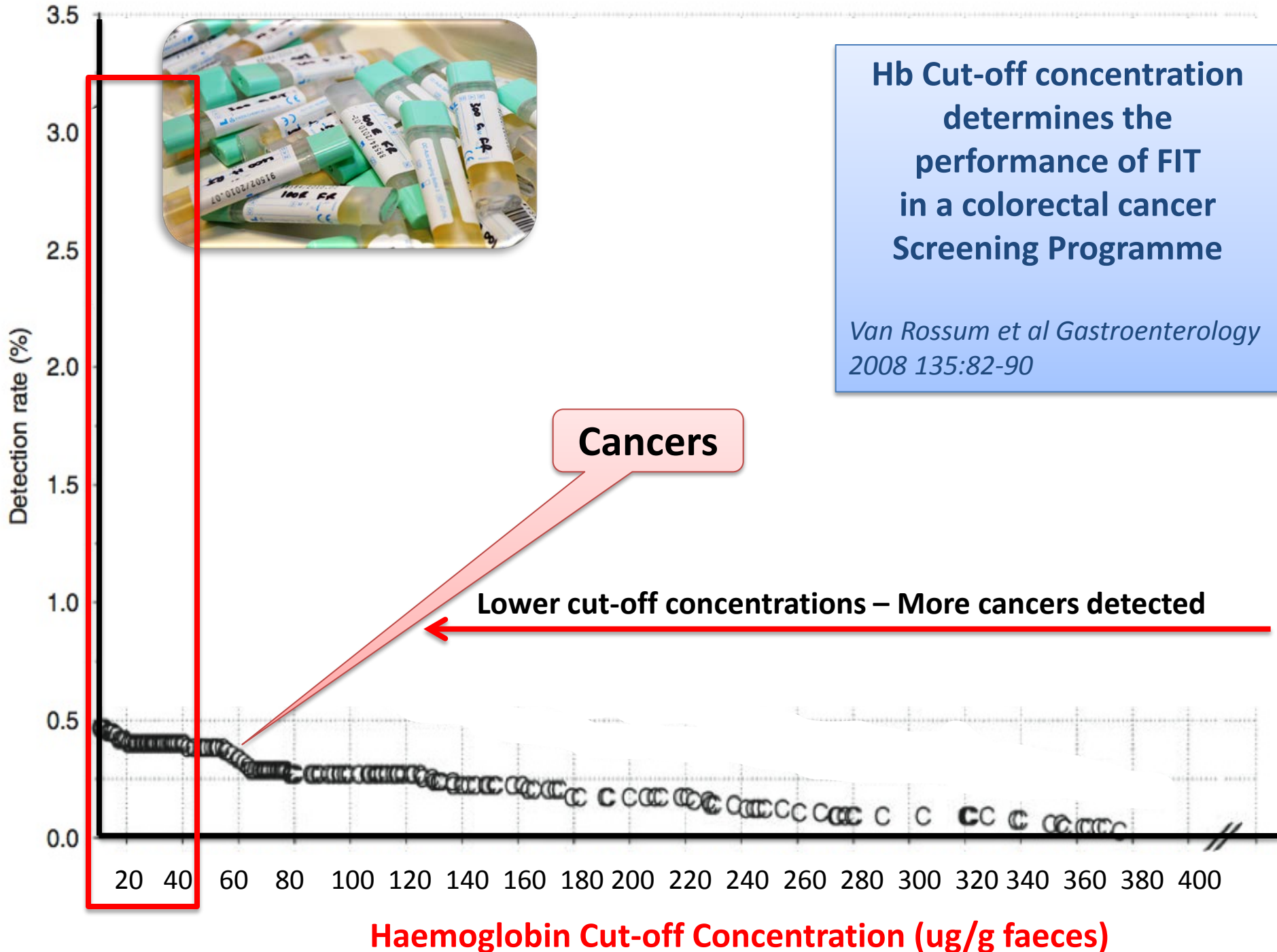
Hemoccult-II and OC-SENSA MICRO

Endoscopic Classification	No. of Patient Outcomes	Positive gFOBT	Mean FIT Conc. ug/g	Positives at 15 ug/g Cut-off	Positives at 20 ug/g Cut-off
<b>Stage</b>	13				
Dukes A & B	10 (77%)	3 (30.0%)	138	9 (90.0%)	8 (80.0%)
Dukes C & D	3 (23%)	1 (33%)	281	3 (100%)	3 (100%)
<b>Site</b>					
Proximal	11 (85%)	3 (27%)	167	10 (90.9%)	10 (90.9%)
Distal	2 (15%)	1 (50.0%)	191	2 (100%)	1 (50.0%)



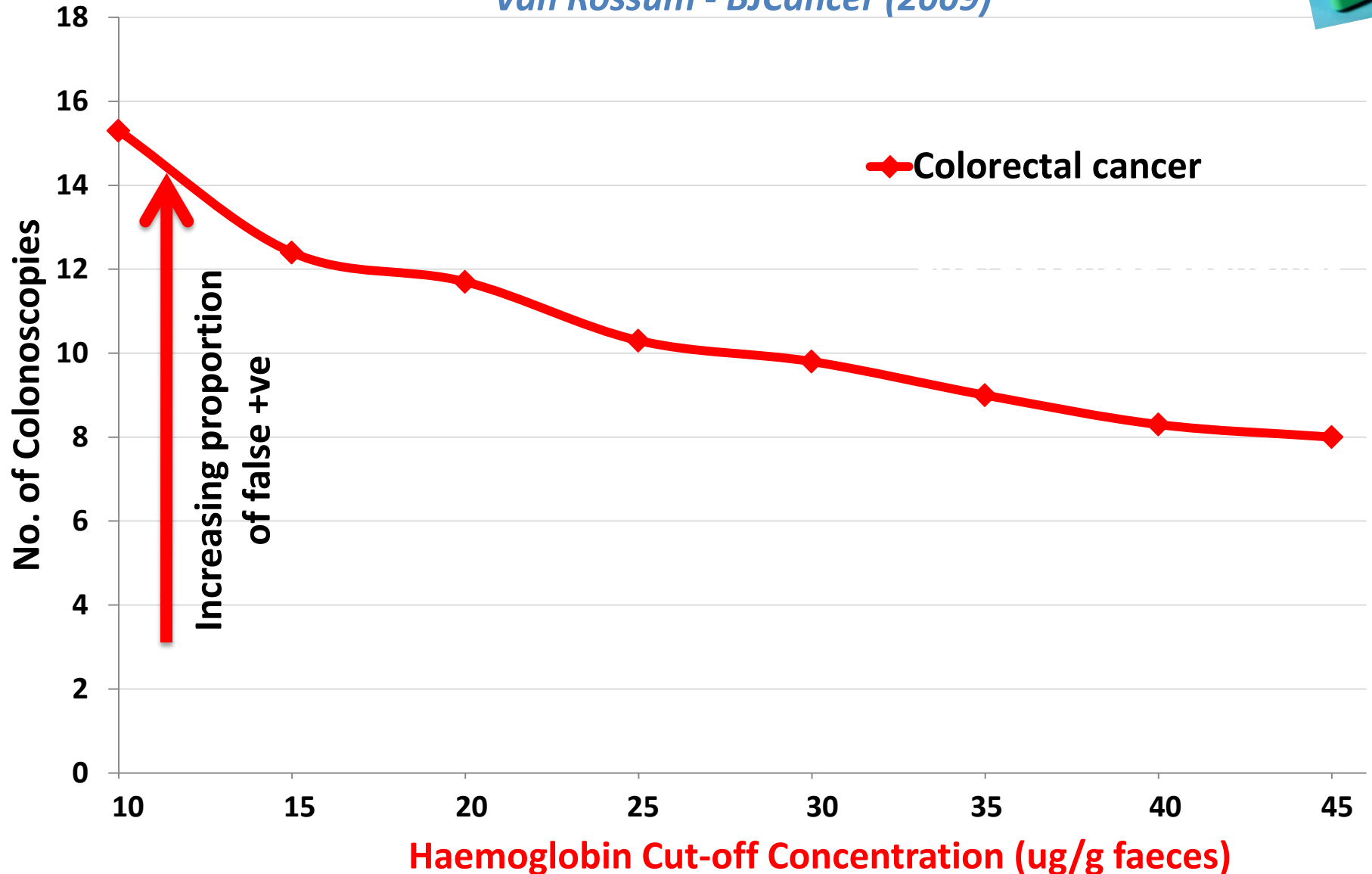
**Hb Cut-off concentration  
determines the  
performance of FIT  
in a colorectal cancer  
Screening Programme**

*Van Rossum et al Gastroenterology  
2008 135:82-90*



# Effect of Cut-off on Number needed to Scope

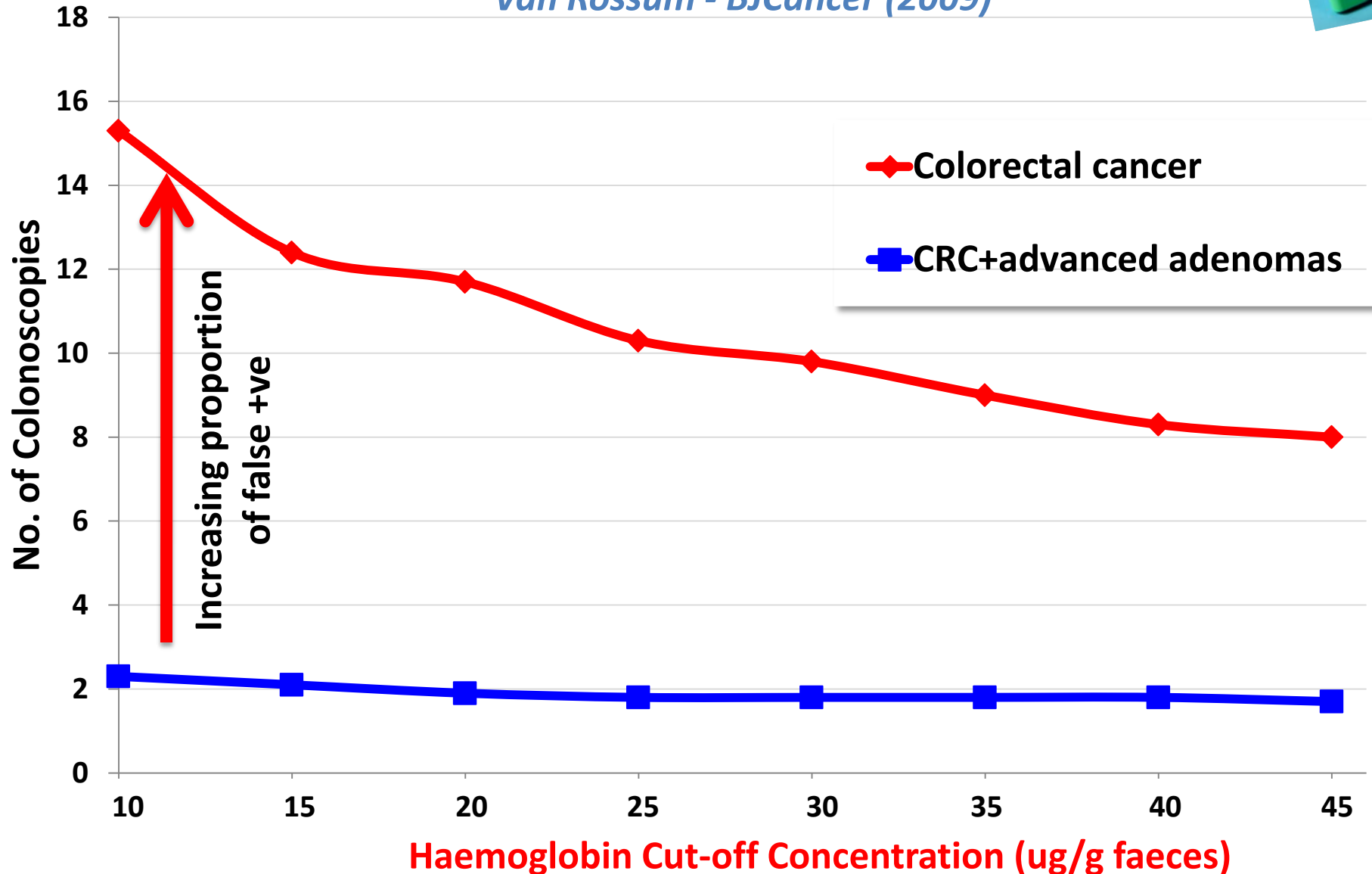
*Van Rossum - BJCancer (2009)*



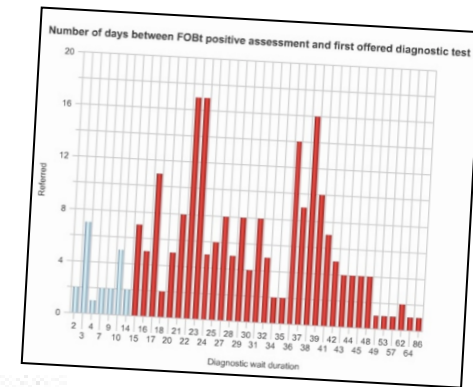


# Effect of Cut-off on Number needed to Scope

*Van Rossum - BJCancer (2009)*



Wait  
Here For Your  
Colonoscopy



Use **quantitation** to adjust  
for endoscopy resource

‘Age? You mean now... or when we first sat down?’



## First hospitals in B.C. colon cancer screening program swamped with referrals

### Rollout delayed in rest of province after facing challenges in Victoria

BY PAMELA FAYERMAN, VANCOUVER SUN    JULY 22, 2013

The much-ballyhooed provincial colorectal cancer screening program. The government first announced the program months ago. But two hospitals in Victoria, space, doctors and nurses that the government. "From what I understand, VIHA put up with it, but it turned out, there were renovations going on, and not enough nurses trained to assist in the program. "So they did it, and then they bumped into the availability of ORs," he said. While the provincial program was supported in the Lower Mainland, the North and the Interior in the province. Terry Lake said other health authorities are learning from the experience. "We've talked to the other health authorities and they may not have the same challenges in other parts of the province. We need to make sure that they're all ready to go when we roll it out. Dr. Max Coppes, CEO of the BC Cancer Agency, said the program will maintain a registry, and set quality assurance standards. "In hindsight, our modelling projections underestimated the challenges of the program."



"We've talked to the other health authorities. So now when we roll it out elsewhere, we do know some of the challenges that will need to be overcome," said Health Minister Terry Lake.

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lement the



## Study Cohort

15,011

Invited

**gFOBT**

5004

**FIT**

5007

Participation

2,351

(49.5%)

2,070

(61.5%)

20ug/g  
Cut-off

Positive test

65

(2.8%)

143

(4.8%)

Follow-up  
examination

62

(95%)

137

(96%)

Advanced  
adenomas &  
cancers

28

(1.2%)

73

(2.5%)

Detected  
cancers

6

(0.3%)

14

(0.5%)

False  
Positives

34

(55)

64

(47%)

## Study Cohort

20,623

Invited

**gFOBT**

10,301

**FIT**

10,322

Participation

4,836

(47%)

6,157

(60%)

20ug/g  
Cut-off

Positive test

117

(2.4%)

339

(5.5%)

Follow-up  
examination

103

(88%)

280

(83%)

Advanced  
adenomas &  
cancers

57

(0.6%)

145

(1.4%)

Detected  
cancers

11

(0.1%)

24

(0.2%)

False  
Positives

46

(45%)

135

(48%)



# Screening for colorectal cancer

<b>FIT (10ug/g cut-off)</b>	<b>Sensitivity (CI)</b>	<b>Specificity (CI)</b>	<b>PPV (CI)</b>	<b>NPV (CI)</b>
<b>Cancer</b>	<b>88</b> (47-99)	<b>91</b> (89-92)	<b>6</b> (3-12)	<b>100</b> (99-100)
<b>Advanced neoplasia</b>	<b>38</b> (29-47)	<b>93</b> (92-95)	<b>37</b> (29-46)	<b>93</b> (92-95)



# FIT sensitivity Left and Right-sided lesions

## Study

T De  
Wijkerslooth  
2011

## Colonoscopy

1256

## Advanced Adenoma

119

Left

38% (29-47)

Right

37% (28-46)

De Wijkerslooth T  
et al. DDW 2011



## Study

Haug U  
2011

## Colonoscopy

2310

## Advanced Adenoma

228

Left

33% (26-41)

Right

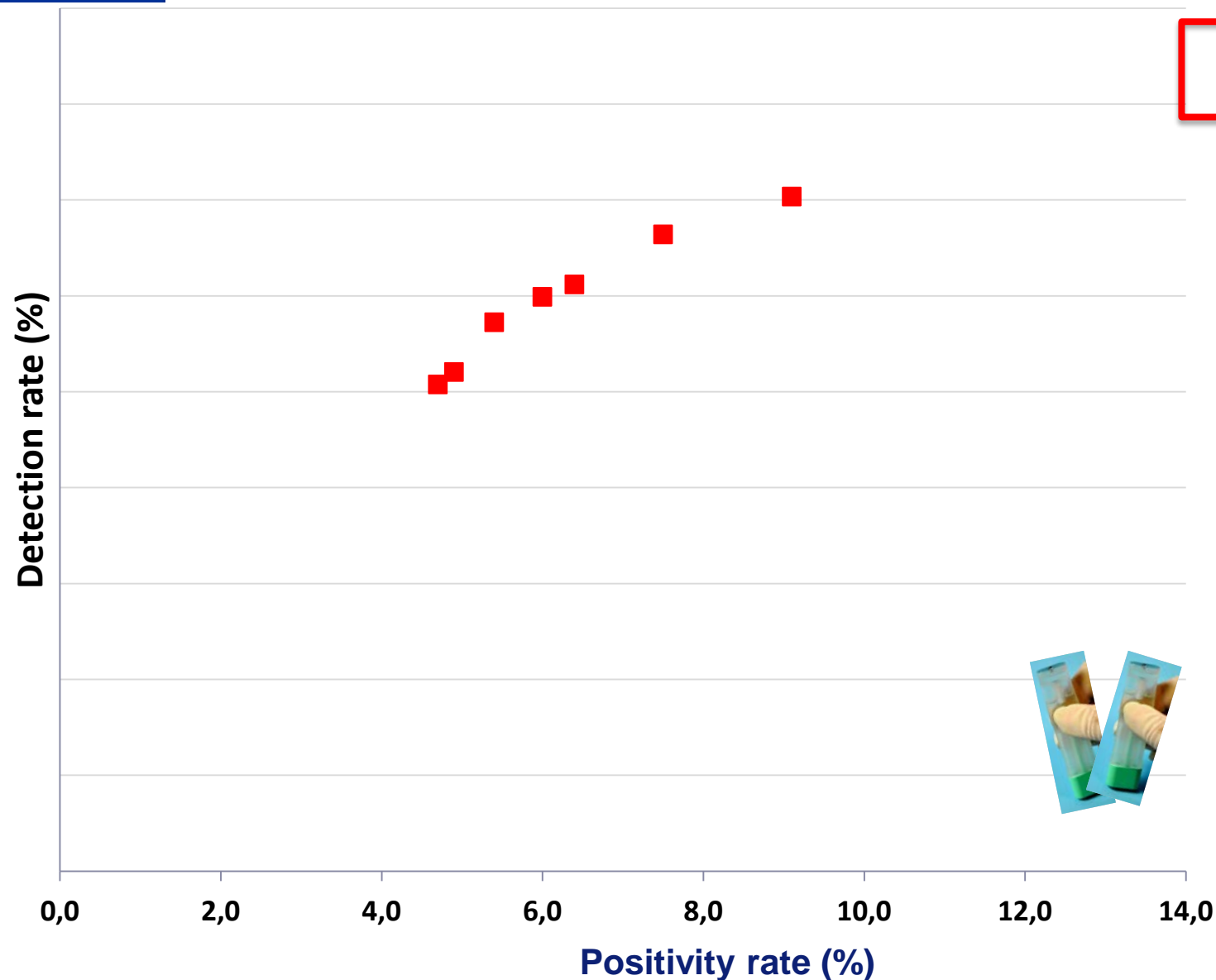
20% (11-31)

Haug U et al.  
Br J Cancer 2011

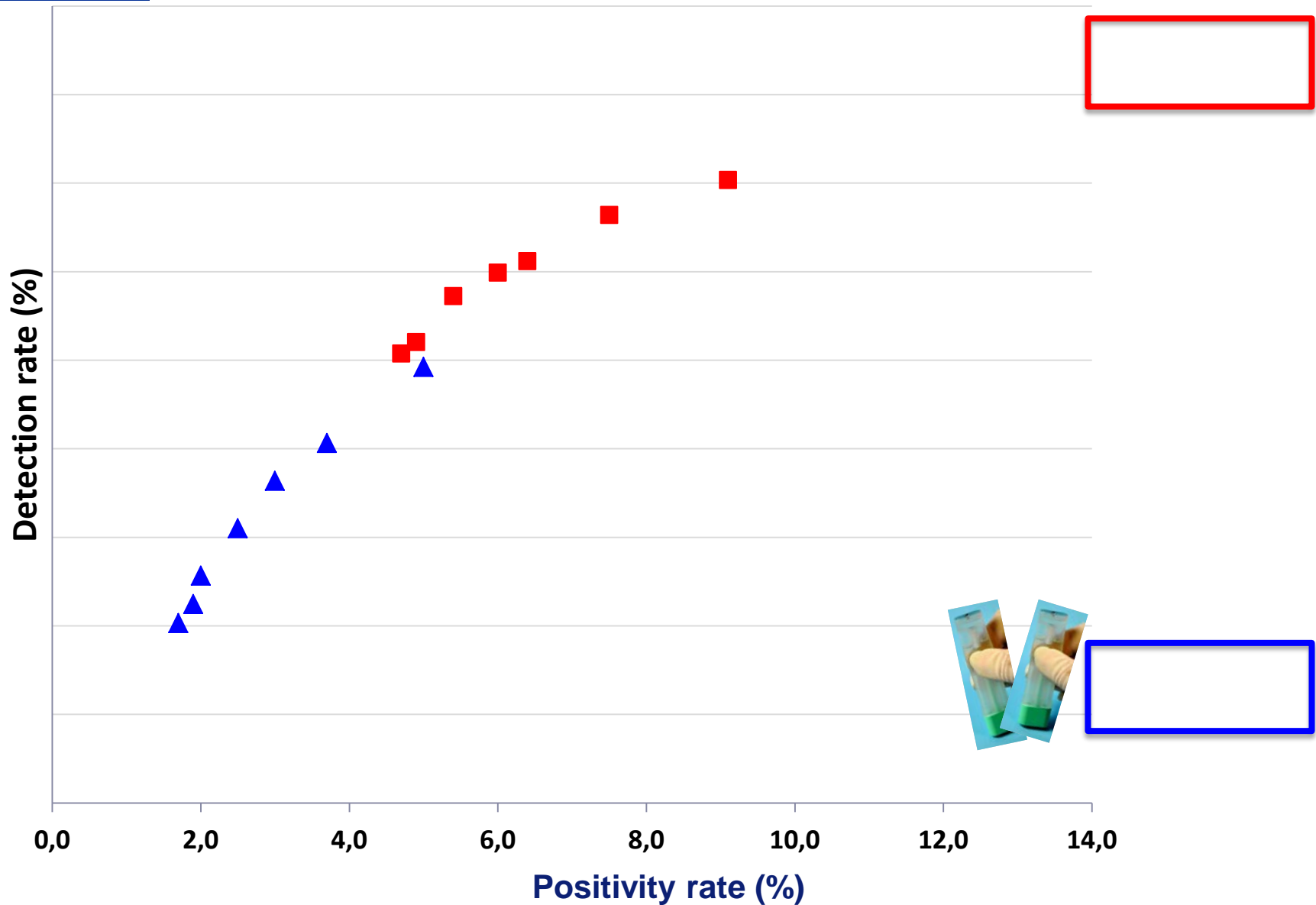




# Detection rate with 1 or 2 day FIT screening

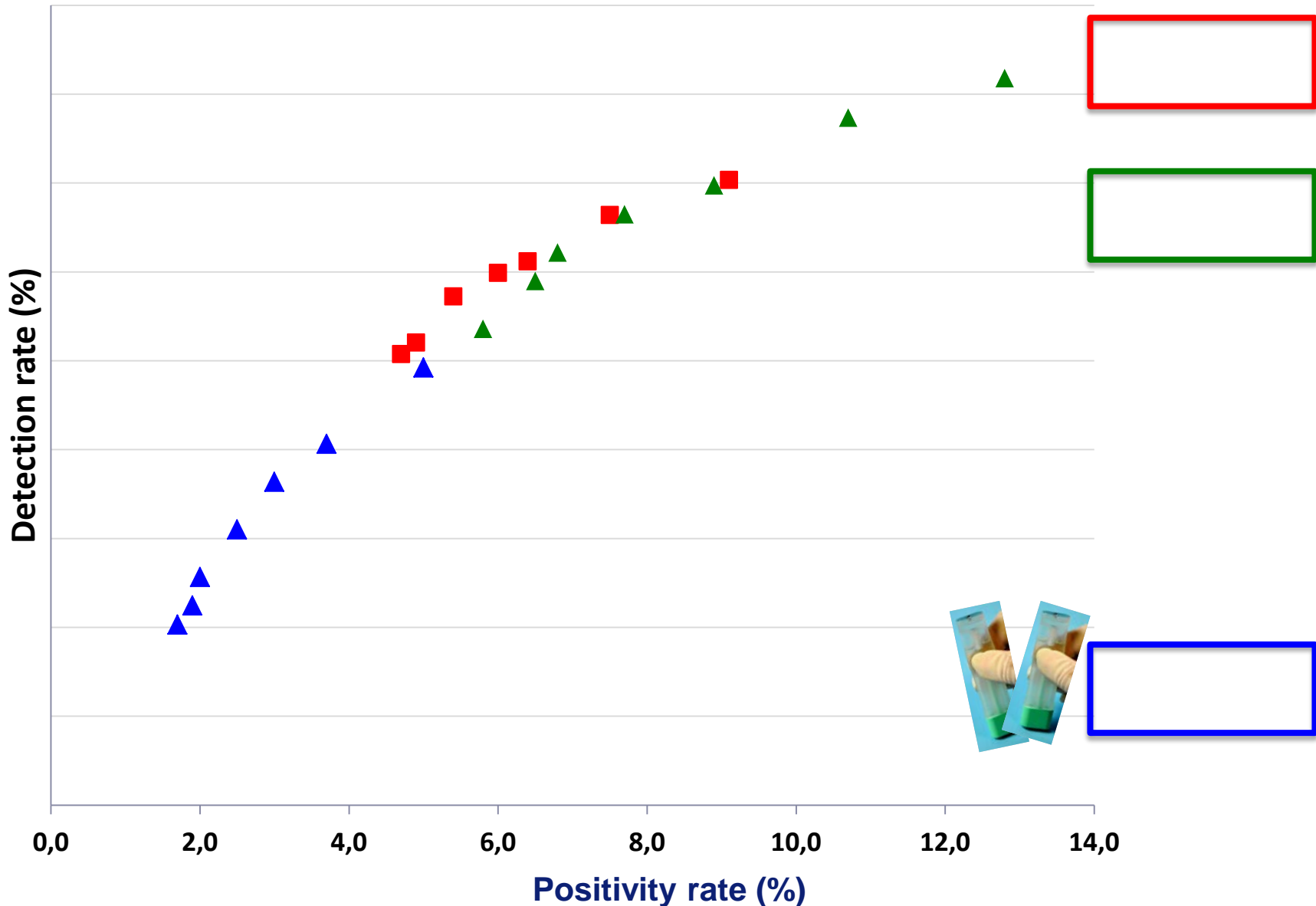


# Detection rate with 1 or 2 day FIT screening





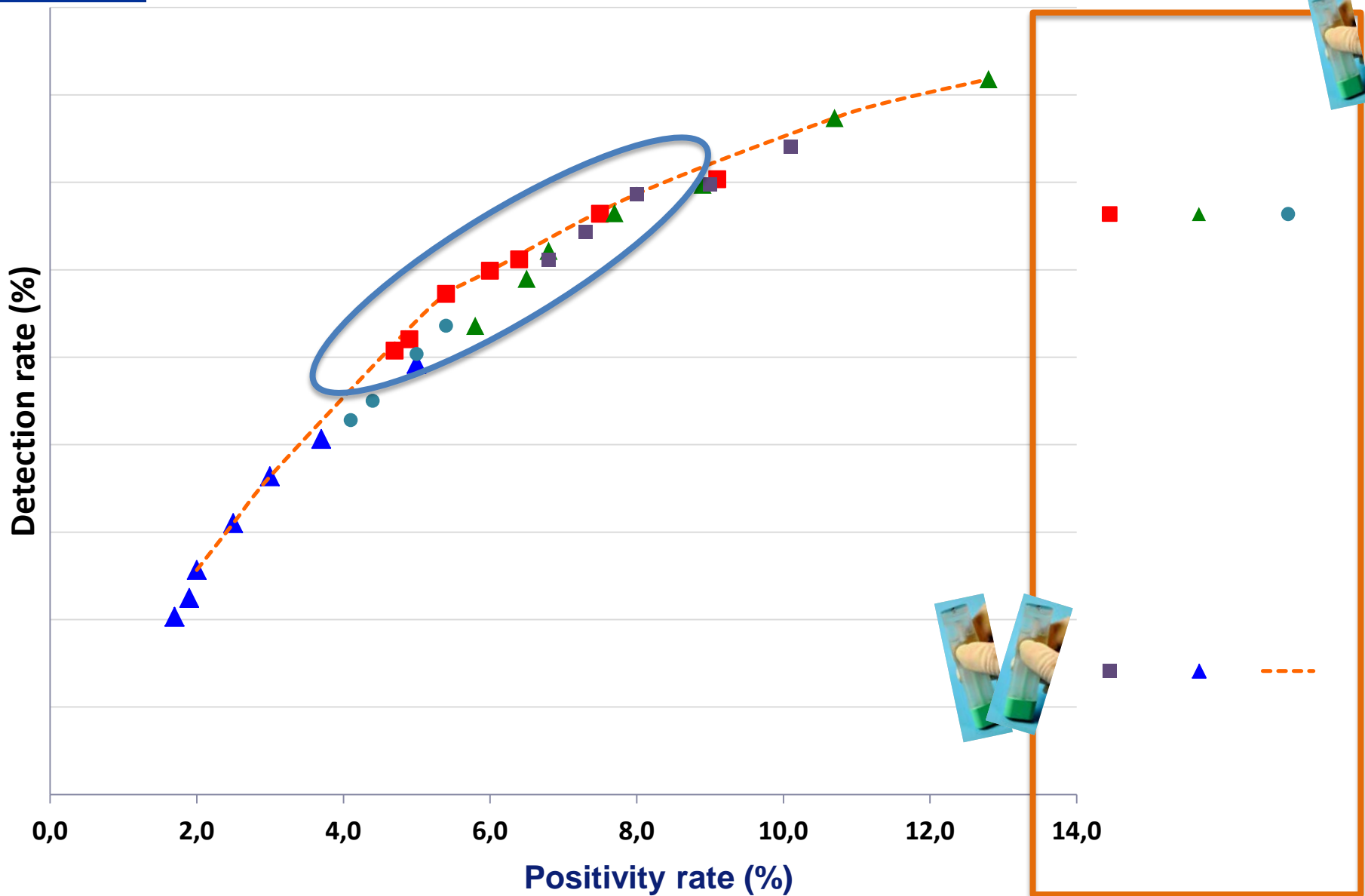
# Detection rate with 1 or 2 day FIT screening

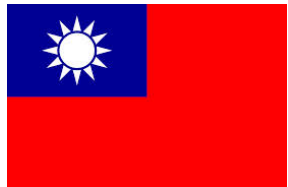






# Detection rate with 1 or 2 day FIT screening



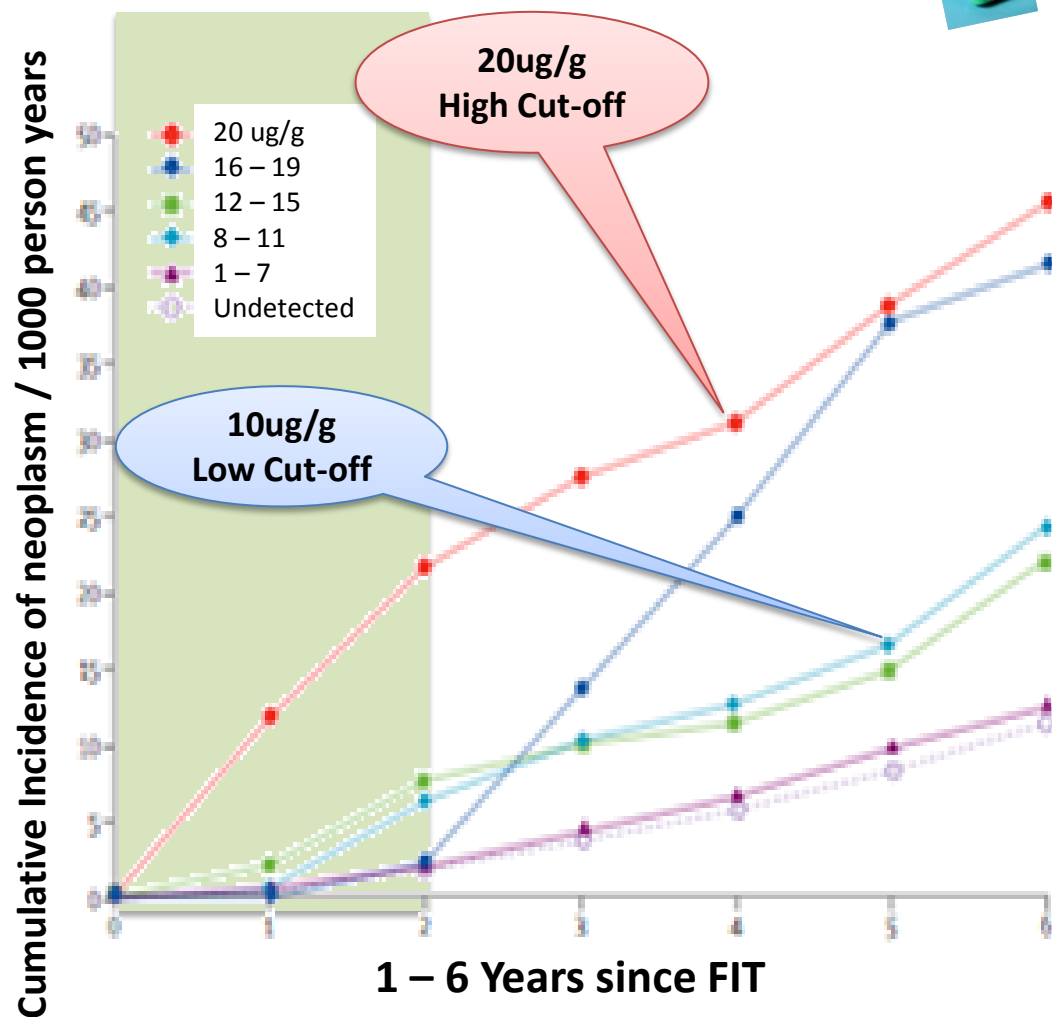


# FIT Cut-off Predicts Incident cancers Taiwanese Population Screening Cohort



## Prospective cohort study

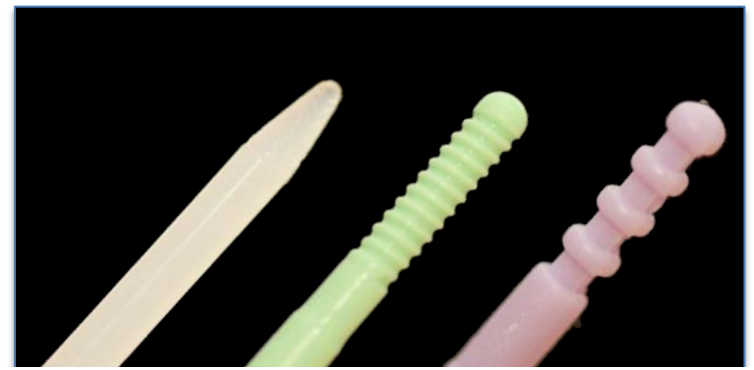
- 2001 and 2007
- 45,992 participants







# Units of measurement and reporting

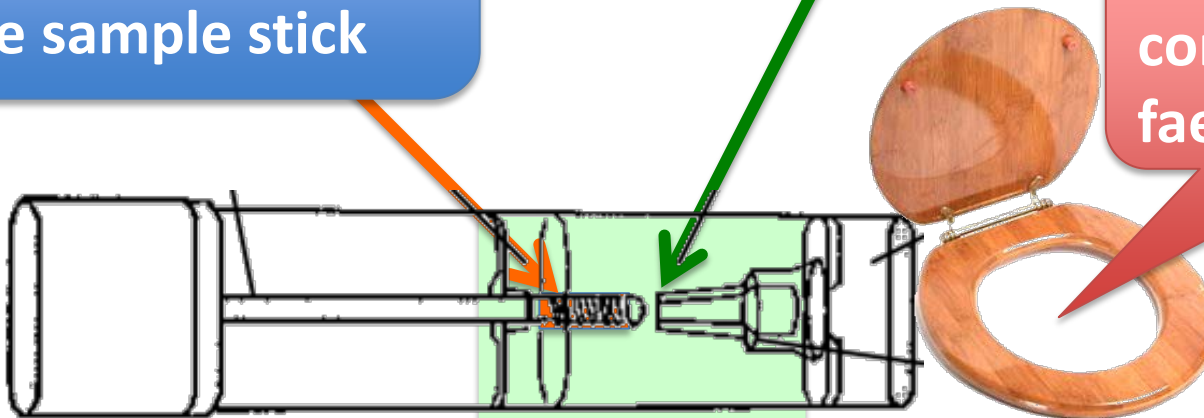


$\mu\text{g Haemoglobin /g of Faeces}$   
 $(\mu\text{g/g})$   
 $\text{ng Haemoglobin /mL of Buffer}$

Depends on quantity of faeces collected on the sample stick

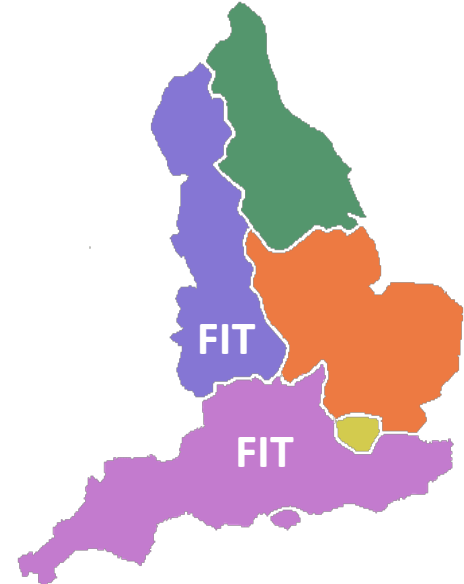
Depends on the volume of buffer provided in the collection device

Interested in the concentration in faeces not buffer!



# FIT and NHS Bowel Cancer Screening in England

## Pilot Design



- FIT *in place* of guaiac FOBT
- 40,000 FIT tests
- Minimal impact upon BCSP
- 1 in 28 invitations will be FIT
- Complete in 6 months
- Use 2 Hubs
- Single kit



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Defining tomorrow, today.™

**VEDA . LAB ...**

**MIZUHO MEDY Co Ltd.**

**BTNX.com**

**KYOWA KIRIN**

**alfresa**

Alfresa Pharma Corporation

**AVENTIR**  
BIOTECH, LLC

**GERMAINE®**  
LABORATORIES, INC.

**CARE** take care!  
diagnostica®

**BIOMERICA**

**ORION**  
DIAGNOSTICA

**SENTINEL**  
DIAGNOSTICS

**SureScreen Diagnostics Ltd**  
Cutting Edge Biotechnology

**Human**  
Diagnostics Worldwide

**accutest®**

**FUJIREBIO®**  
Diagnostics, Inc.

**TREMBLAY HARRISON**

**Alere™**

**Medix Biochemica**

**preventis**

**M**

**EIKEN CHEMICAL CO., LTD.**  
**41 Companies**  
**Contacted**

**alfa**  
SCIENTIFIC DESIGNS, INC

**r-biopharm**

**A.MENARINI**  
diagnostics

**ulti med**

**Cima**  
Gesellschaft für Diagnostika mbH

**Lobeck Medical Ltd**

**EPITOPE DIAGNOSTICS**  
QUALIFIED TESTING KIT MANUFACTURER

**CLIAwaived™**  
.com

**immunostics, inc.**

**Quest**  
Diagnostics

**BECKMAN COULTER**

**innovacon™**

**QUIDEL®**  
CORPORATION

**MP**

**BIOHIT HealthCare**  
Innovating for Health

**InSure® FIT™**  
Fecal Immunochemical Test

**ELITechGroup**  
ELITech UK

**TC** **Teco Diagnostics**  
Clinical Specialists

**LINEAR**  
**HEMOSURE®**



# Available FIT Systems

FOB Gold NG/ BioMajesty



NS PLUS-C15



HM-JACKarc

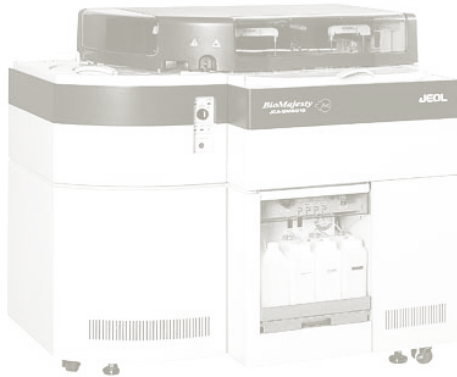


OC Sensor DIANA



# FIT System for NHS Pilot

FOB Gold NG/ BioMajesty



NS PLUS-C15



HM-JACKarc



OC Sensor DIANA



# FIT System for NHS Pilot

FOB Gold NG/ BioMajesty



NS PLUS-C15



HM-JACKarc



OC Sensor DIANA

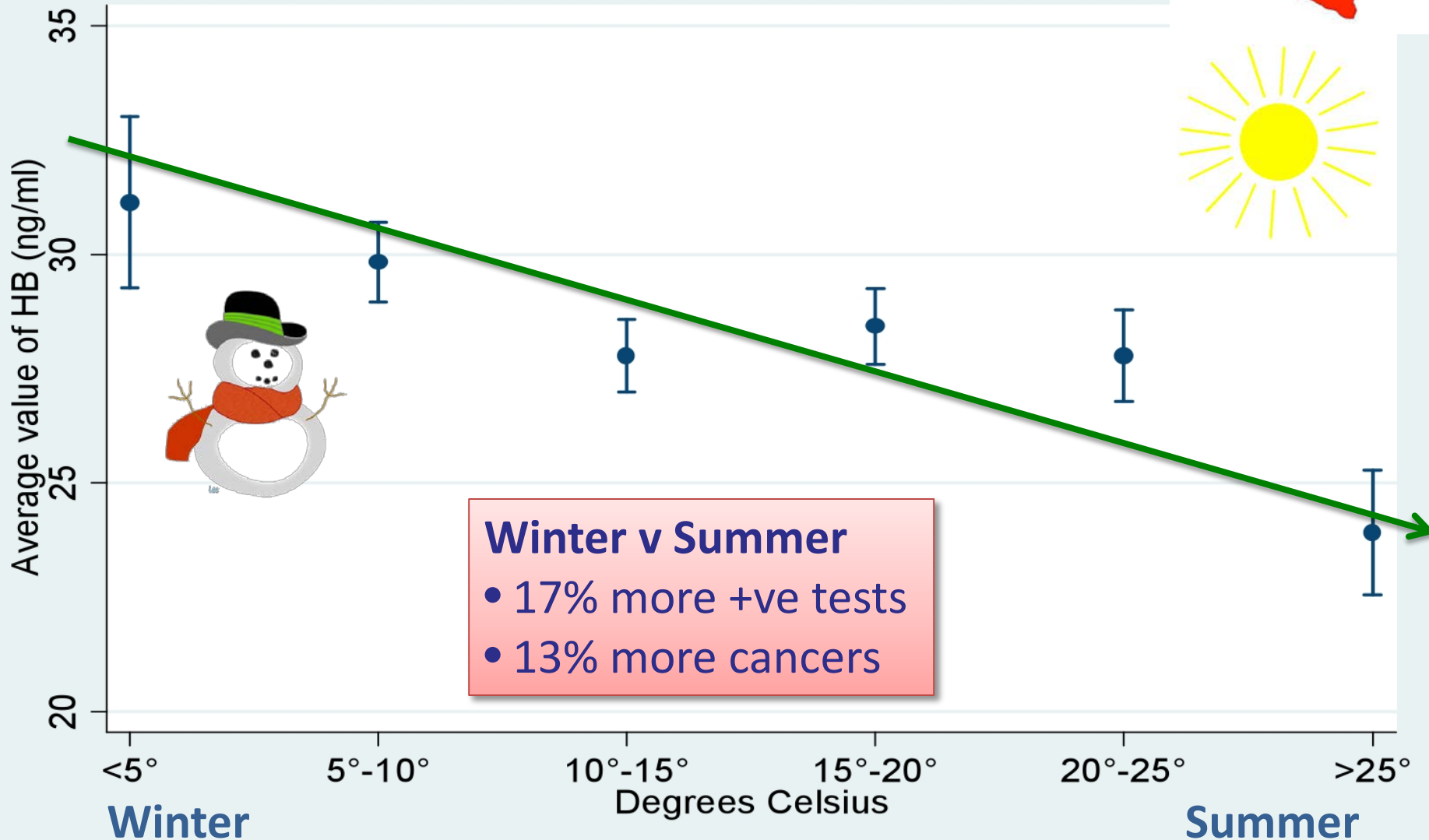


# Stability of FIT (OC Sensor)

*Grazia Grazzini et al Gut. 2010 Jul 5*

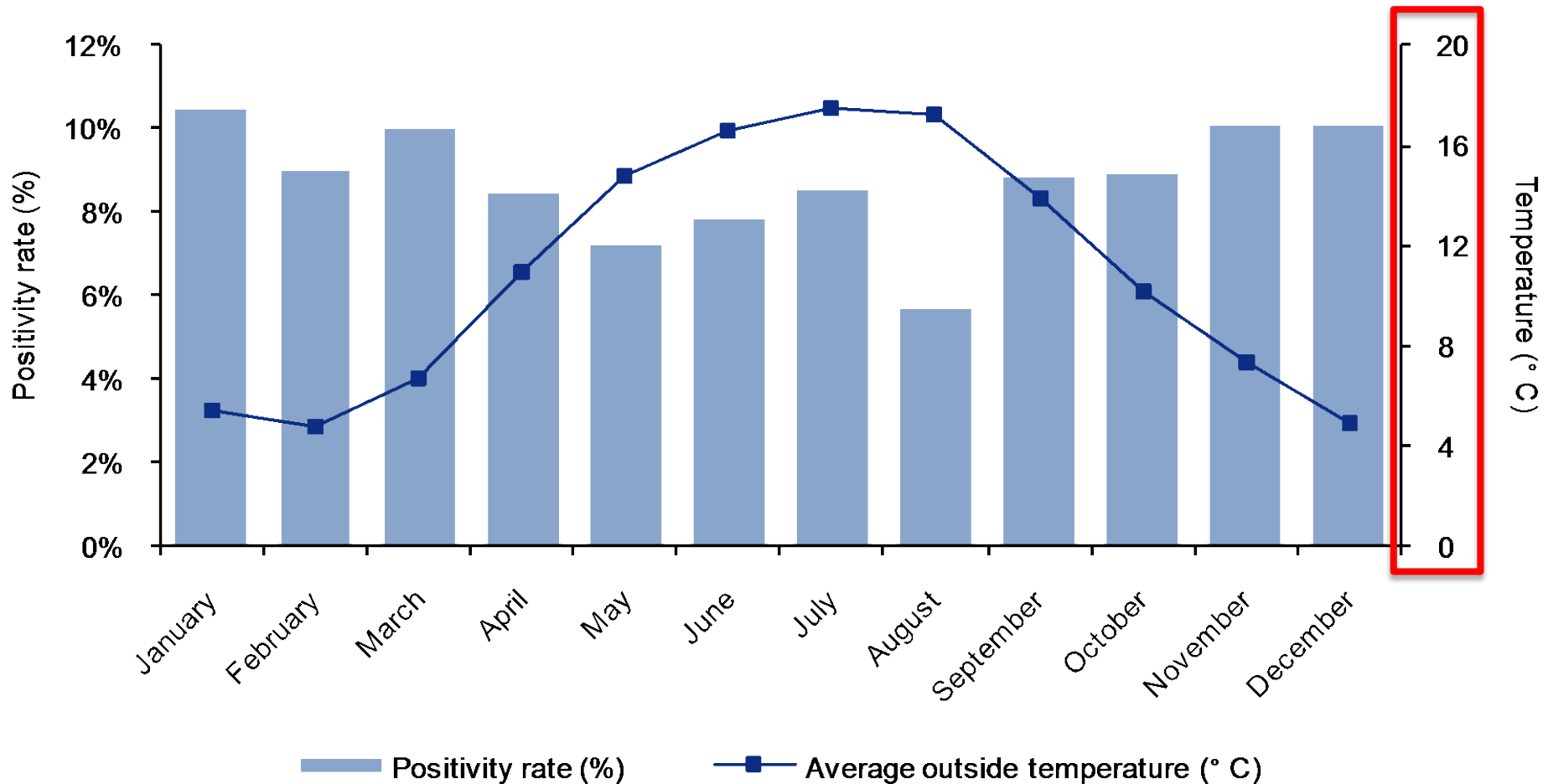


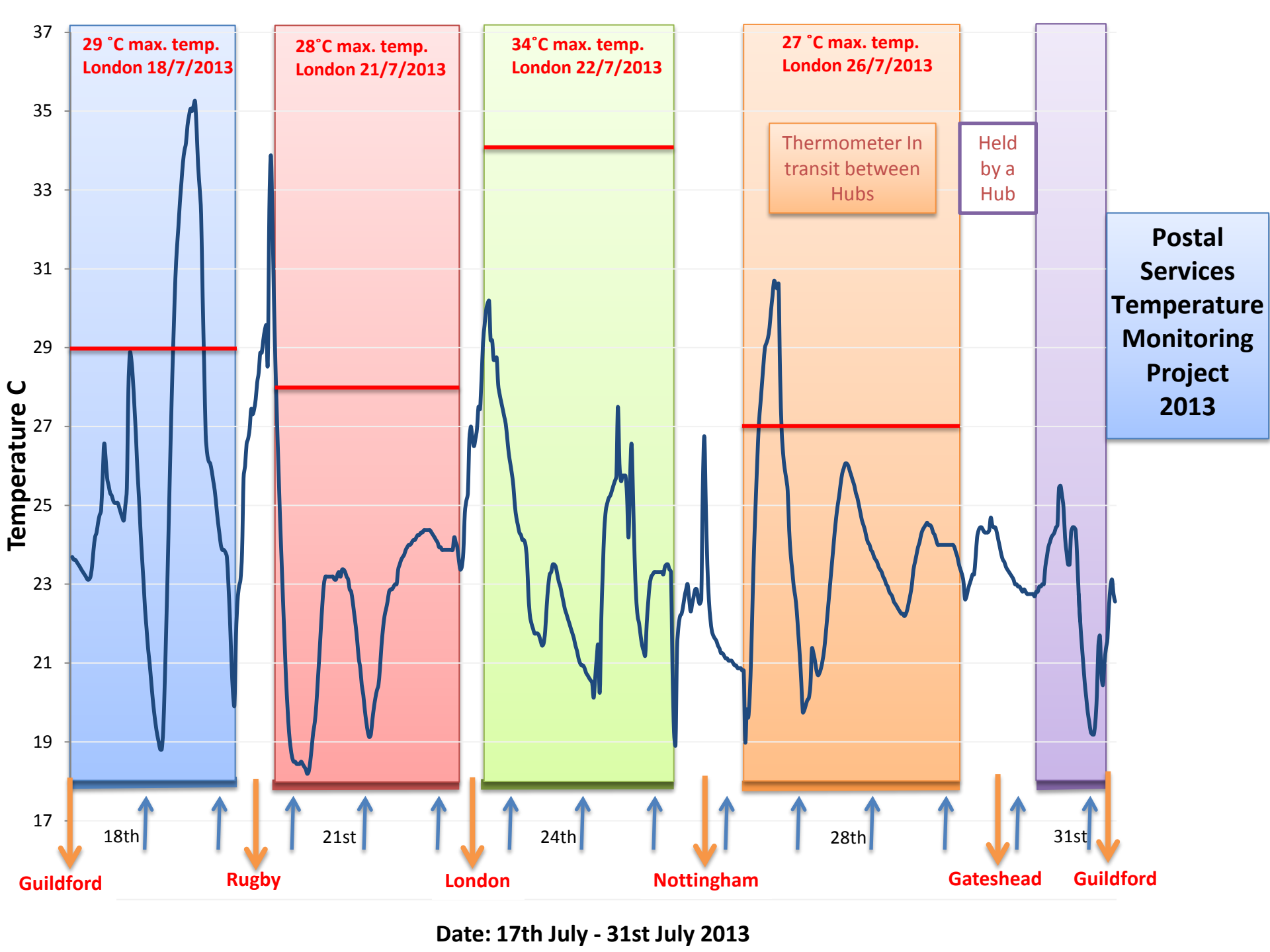
Average value of HB in intervals of 5° Celsius



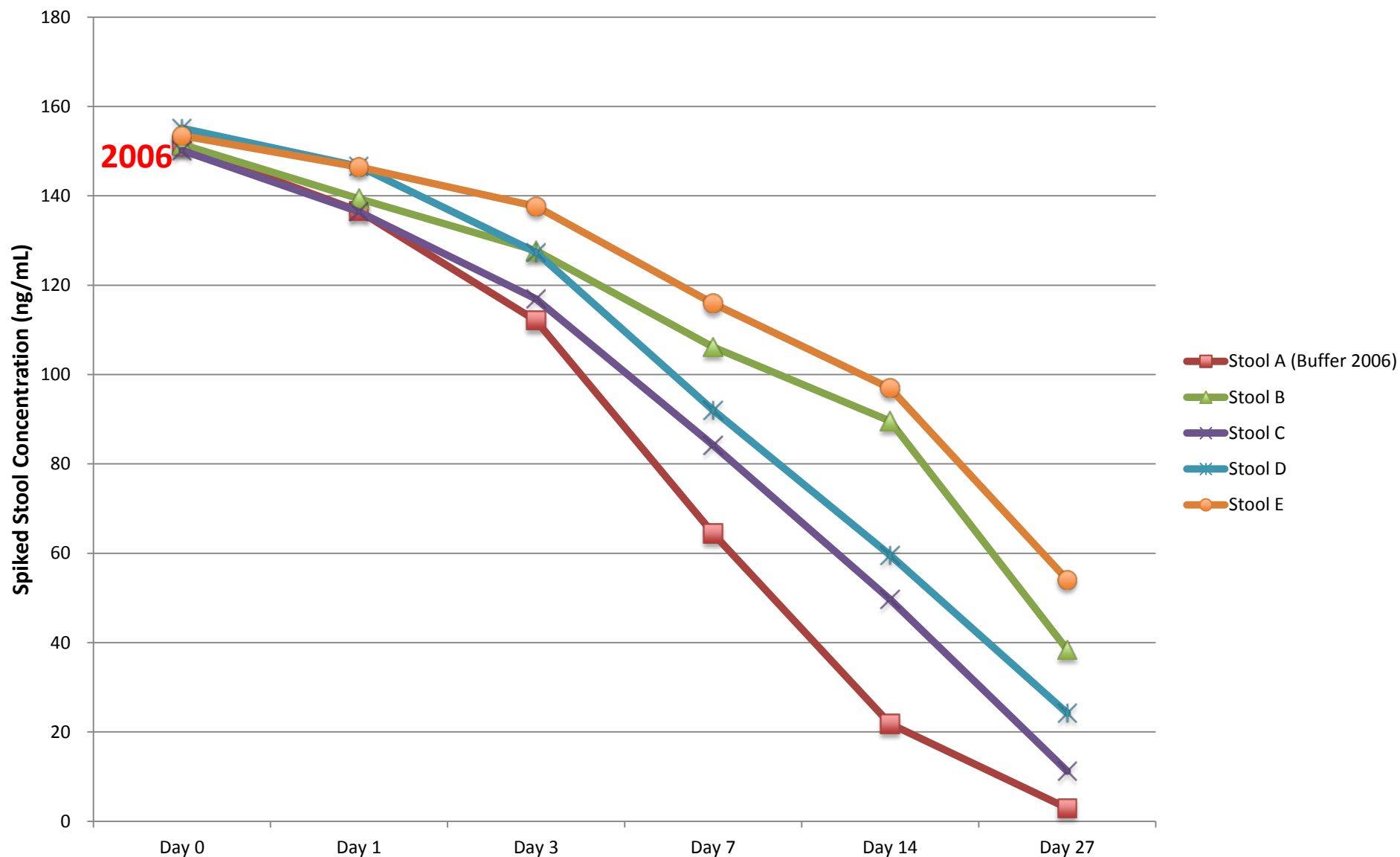


# Seasonal variation in positivity rates in the Netherlands

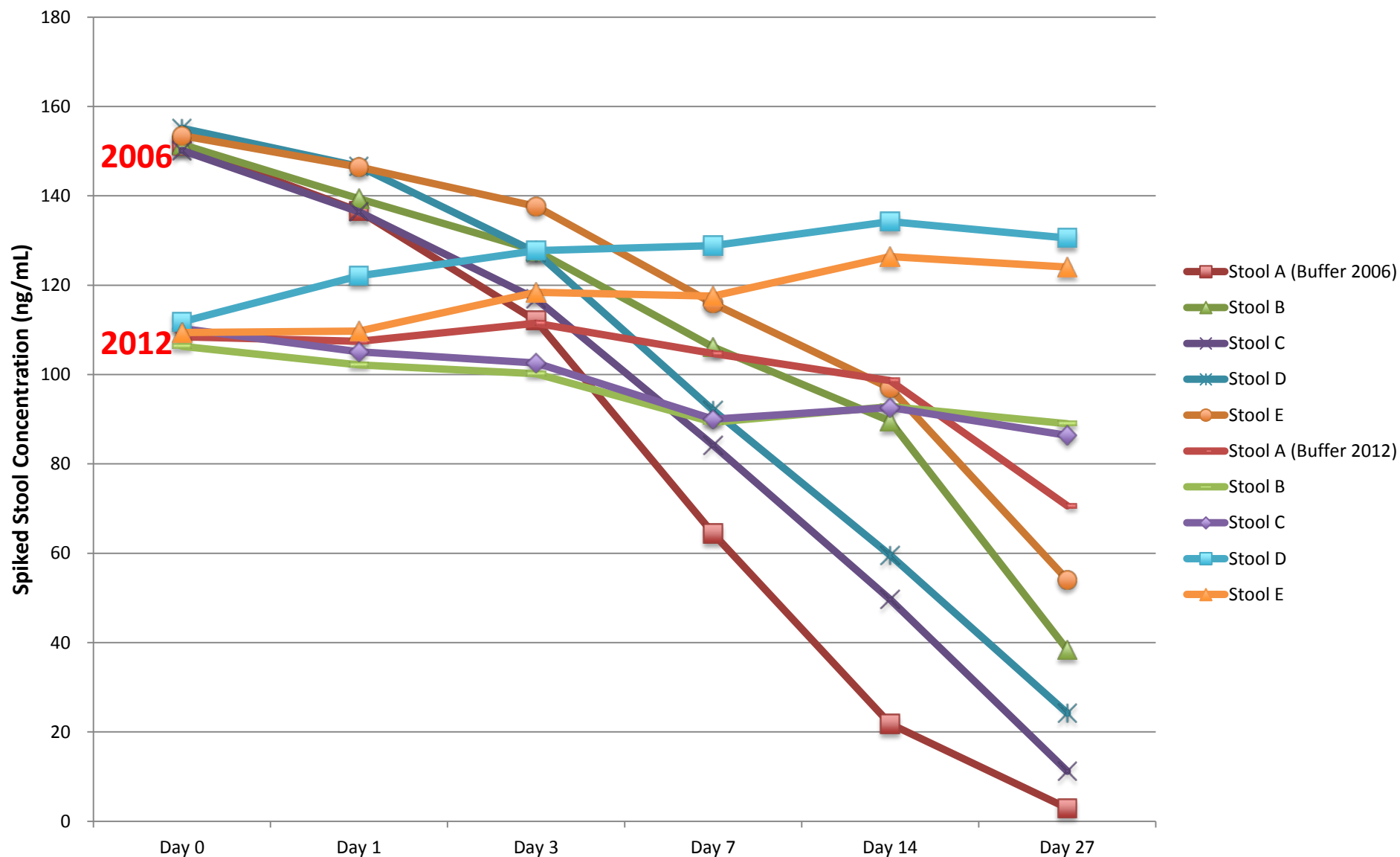




Individual Stool Samples  
Spiked to **150** ng/mL  
2006 and **2012** Eiken Buffers at **25°C**



# Individual Stool Samples Spiked to 150 ng/mL 2006 and 2012 Eiken Buffers at 25°C





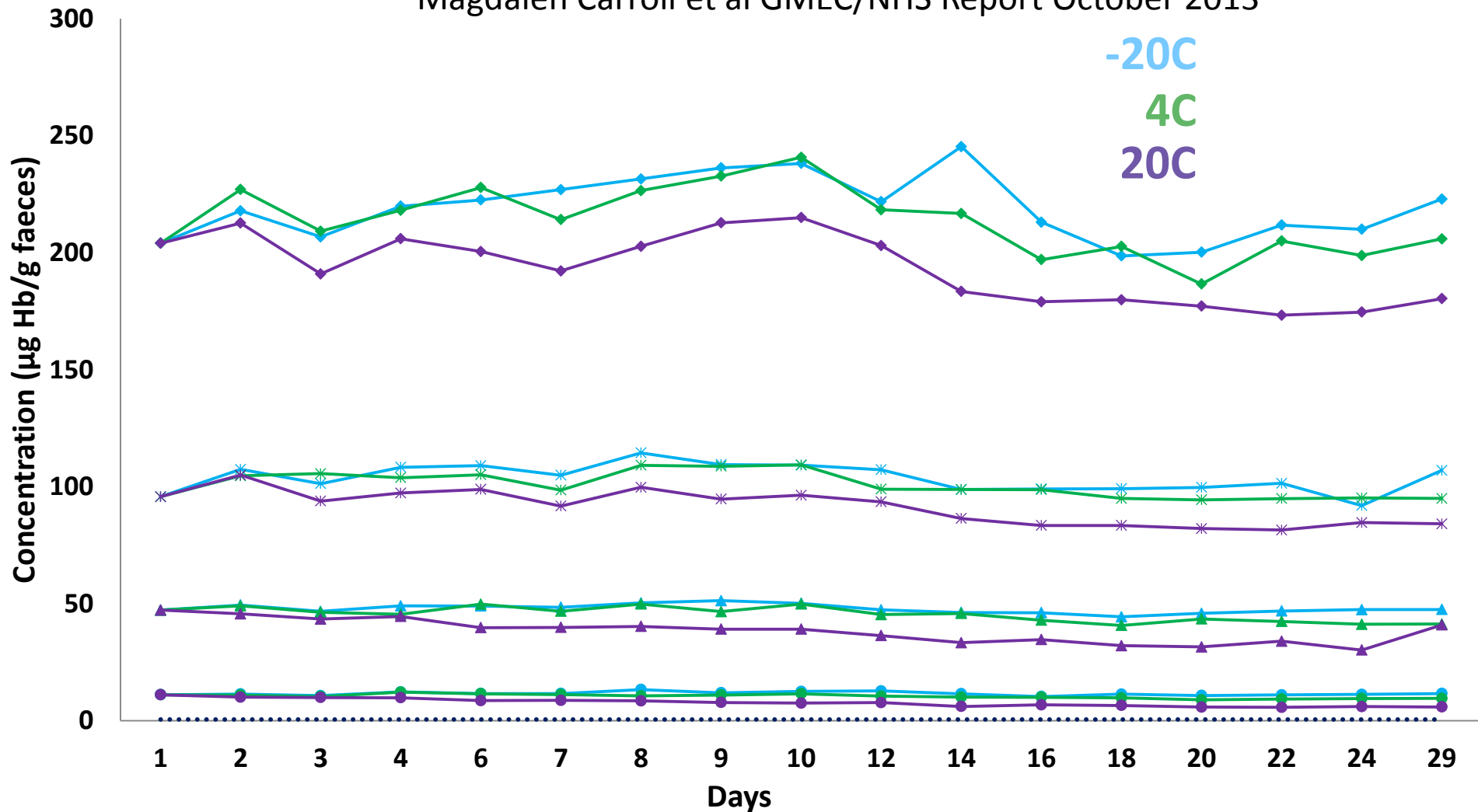


# FIT Stability Studies

HM-JACKarc (*Hb spiked buffer*)



Magdalen Carroll et al GMEC/NHS Report October 2013



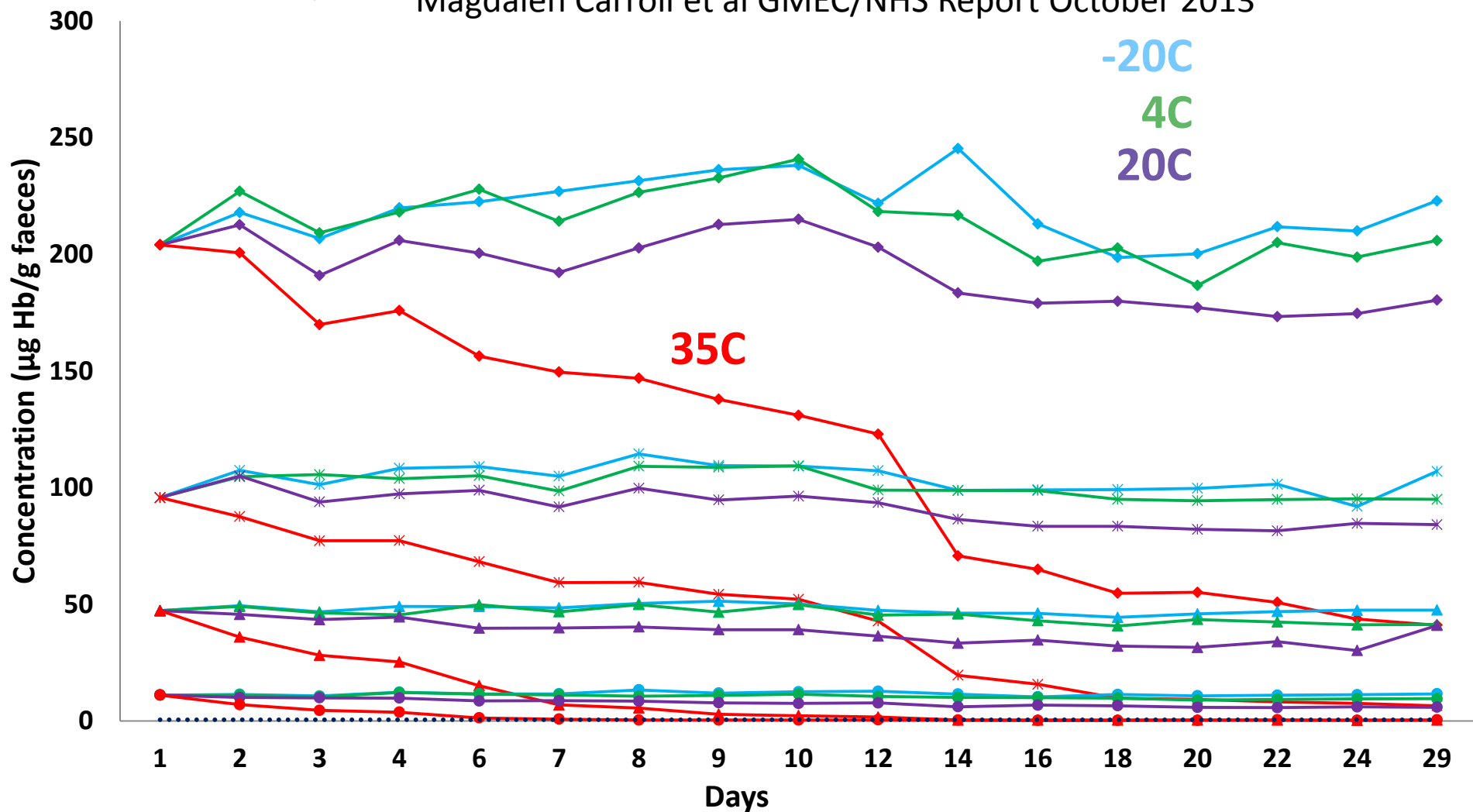


# FIT Stability Studies

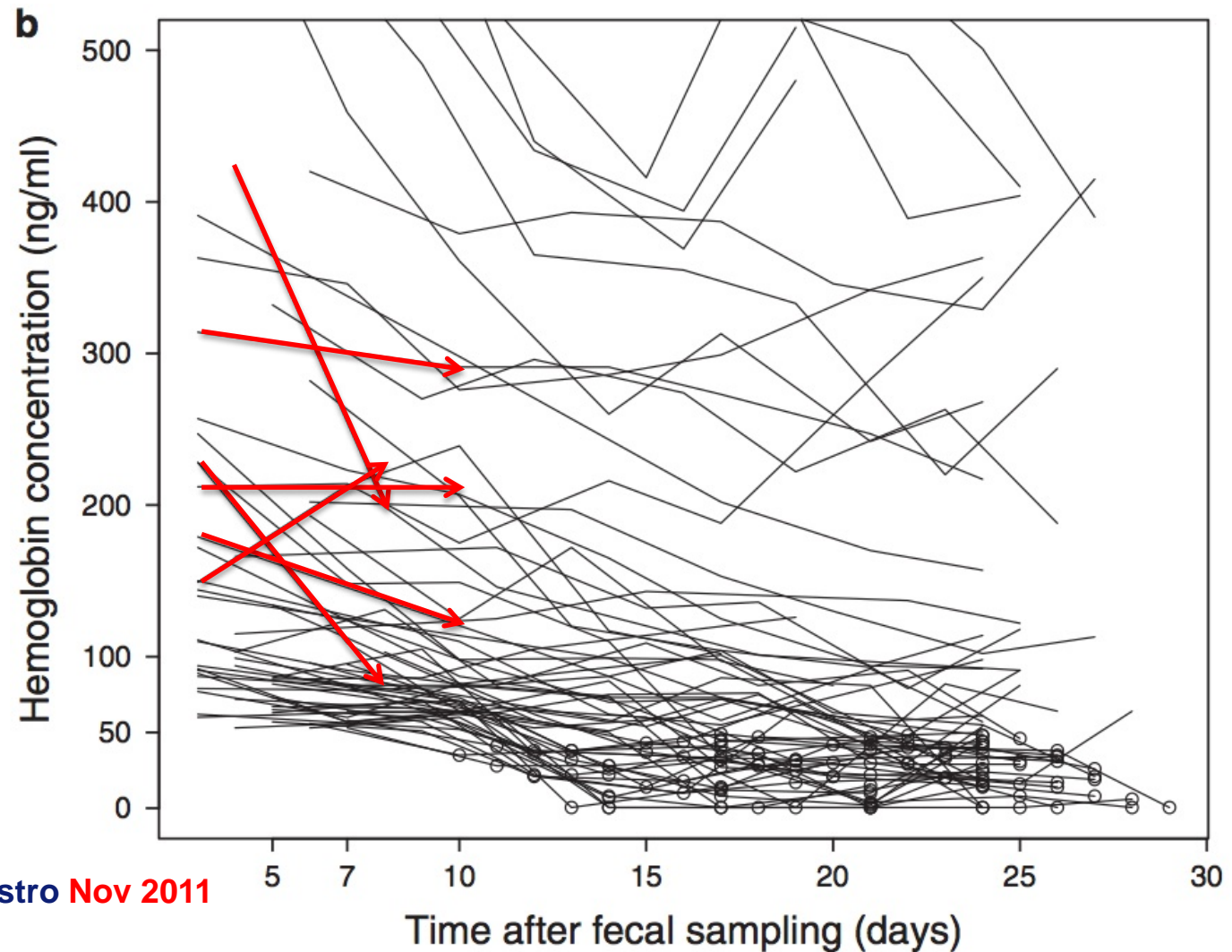
HM-JACKarc (*Hb spiked buffer*)



Magdalen Carroll et al GMEC/NHS Report October 2013



# Stability of FIT - Lab Experiment



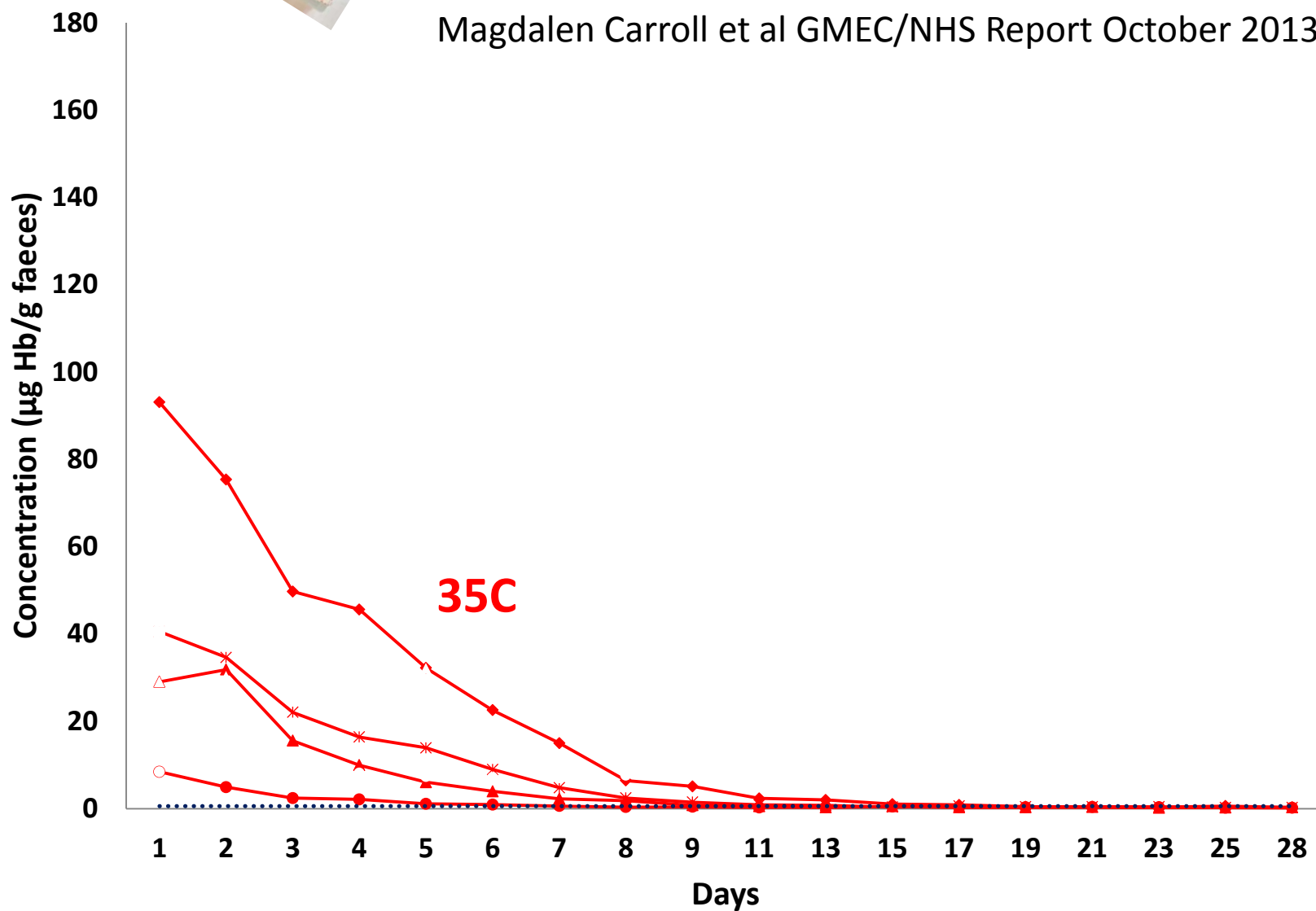


# FIT Stability Studies

HM-JACKarc (*Hb spiked faeces*)



Magdalen Carroll et al GMEC/NHS Report October 2013





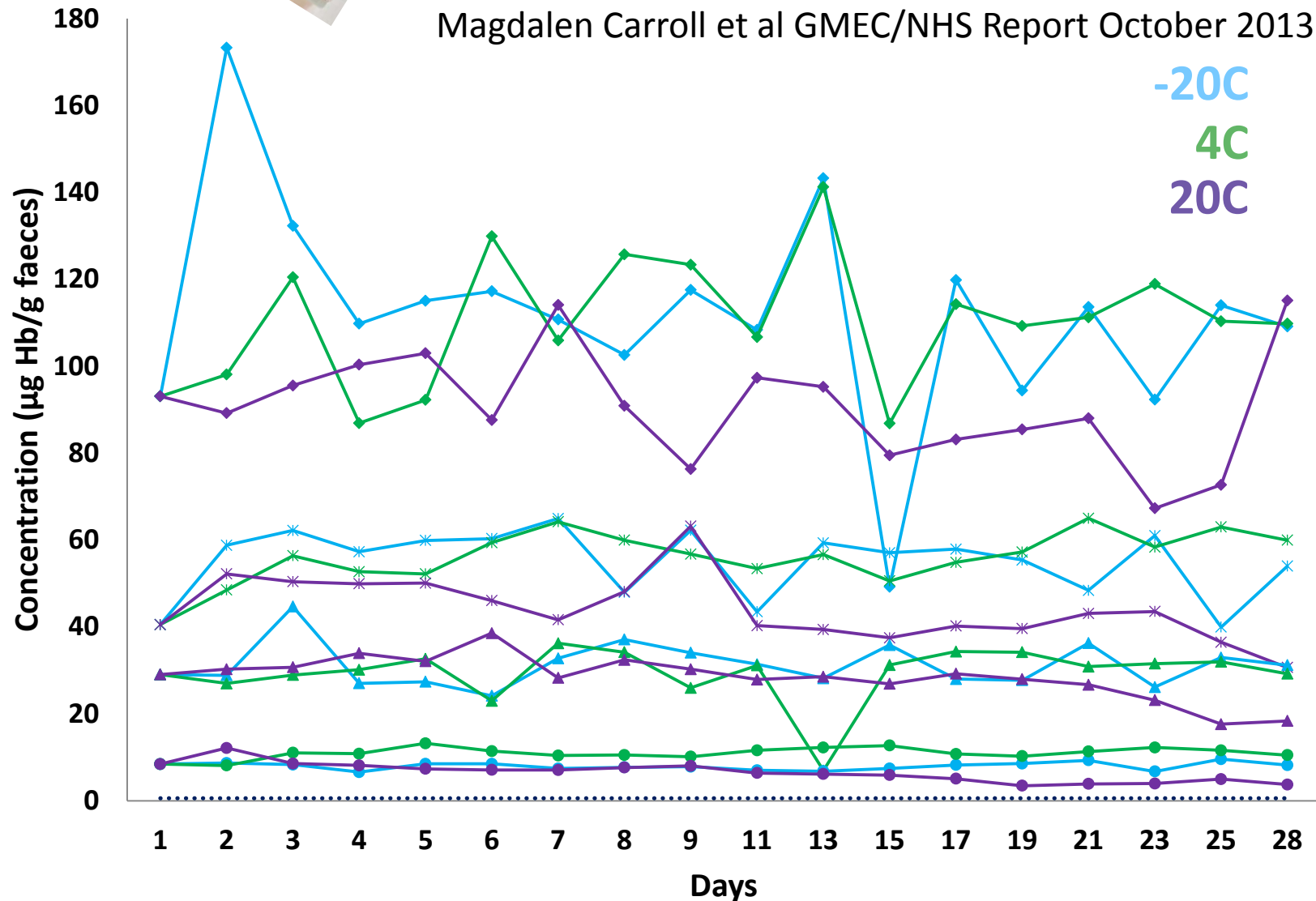


# FIT Stability Studies

HM-JACKarc (*Hb spiked faeces*)



Magdalen Carroll et al GMEC/NHS Report October 2013



# Maximising Uptake

## Miscellaneous

- Change from gFOBT to FIT - 4 to 8% increase
- GP involvement? – depends on GP
- Pre-invitation – 6% already done!
- CO<sub>2</sub> insufflation – comfort factors
- Target local 'Problem Population'

## Test design and packaging

- Elderly – Arthritis, Parkinson's disease etc

## Information

- Learning difficulties – Alternative literature?
- Language – different languages, different letters?
- Braille, sign language, translators, DVD – *Done!*
- ....but avoid excessive information!

## Coverage

- Disabilities – local initiative
- Prisoners



# Maximising Uptake

## Miscellaneous

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## Coverage

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- Prisoners



1

Pull the zip strip from top to bottom...



2

Peel the envelope apart, drag your disc from its pouch, and watch as usual.



3

To return, detach front panel by tearing down crease...



4

Thrust your disc back into the envelope pouch...



5

Peel off the seal strip, fold the flap over, and stick down.



6

Wham it in a post-box, and the magic starts all over again...



# Make packaging

Attractive

Informative

Safe for mailing

Simple to use

Reliable





# Participant



UK Mail

*Hub Return Address*

Bowel Cancer Screening Hub  
20 Priestley Road  
Research Park  
Surrey GU2 7YS



# Screening Hub





# CRC Population Screening

- Good test is one that gets done
- Choice agenda
  - CRC screening menu
- Flexi sigmoidoscopy, colonoscopy, new faecal & blood tests
- **FIT will be the primary tool for CRC screening for next 10-15 years (SPH Prediction)**

## Gastro Central CRC Screening Menu



### Tonight's Specials...

1. Colonoscopy - Chef's Special €800  
Served with midazolam
1. Flexi Sigmoidoscopy €200  
Bring your own enema!



### Takeaway menu...

1. Blood Screen €100  
Be the first to check this one out!
2. New Stool FIT & DNA Test – not yet available
3. FIT €10  
(Free colonoscopy with every positive FIT)

(Free colonoscopy with every positive FIT)

3. FIT €10

2. New Stool FIT & DNA Test – not yet available

Be the first to check this one out!

1. Blood Screen €100

# This is only the beginning...



## Today...

FIT is used as a single risk factor with a simple cut-off

## Tomorrow...

CRC risk will combine FIT with other parameters to provide a new more powerful predictor of colorectal cancer (*?FIT & DNA*)





# Multivariate Risk Scores

## Exploiting the potential of FIT



### Faecal Immunochemical Test for Haemoglobin

- **FIT concentration**
- **Age & Sex**
- **Screening history**
  - Time & outcome of last 3 FIT screens
  - Time & outcome of last colonoscopy/ FS etc
- **Index of Multiple Deprivation**
- Sociodemographic /Geodemographics (*Postcode*)

Available on  
Screening database

Available in  
Clinic / GP

- **Medical History** – IBD, Crohns, DM, etc
- **Family History** – 1<sup>st</sup> and 2<sup>nd</sup> degree relatives
- **Life style** - Smoking, exercise, diet, obesity



# Multivariate Risk Scores

## Exploiting the potential of FIT



**Multivariate  
Bowel Cancer  
Risk Score**

**Improved PPV &  
Cost Effectiveness of  
Colonoscopy Referrals**

Available on  
Screening database

Available in  
Clinic / GP

# FIT – A Good Biomarker & Device?



## Good Design

- Easy to use
- pack
- mail
- test

## Reliable

- Participant
- Lab
- Clinician

## Affordable

- Device
- Package
- Mailing





# FIT for Population Screening...

## Quantitative or Qualitative FIT

- Automated
- Objective measurement
- Positivity tailored to clinical targets and resource
- Monitored analytical performance
  - *Internal Quality Control*
  - *External Quality Assessment*
- Operational performance monitoring
  - *Response monitoring*
  - *Clinical outcome monitoring*
- Combine with other risk factors
- Cheaper... if subject to comprehensive costing





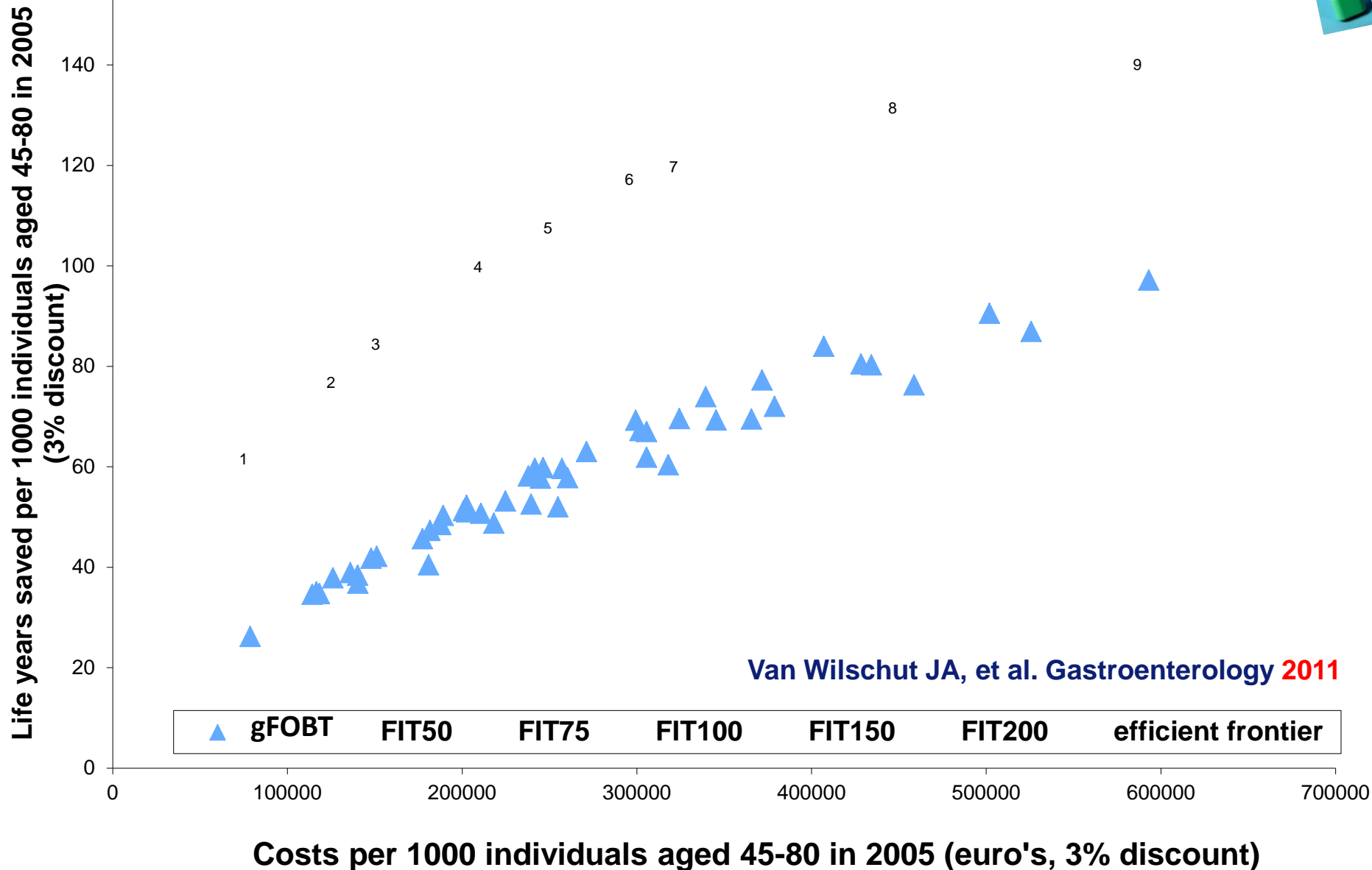
# FIT and NHS Bowel Cancer Screening in England



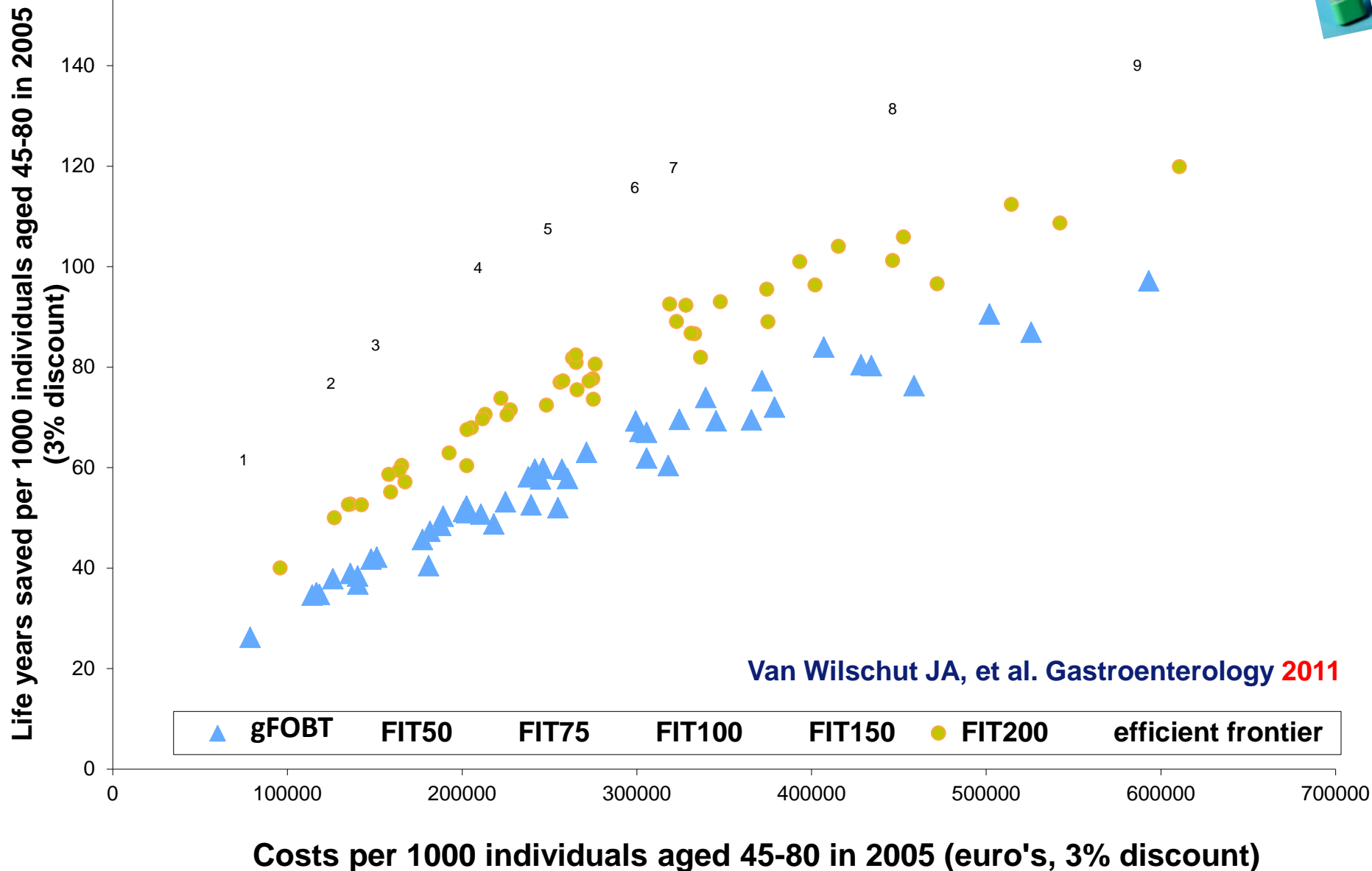
- **2012/13/14** – Preparations for a FIT pilot
  - Pilot design
  - Develop and test FIT programme software
  - Evaluation of 4 FIT systems
- **2014** – FIT Pilot April to October



# Economic modelling of gFOBt and FIT

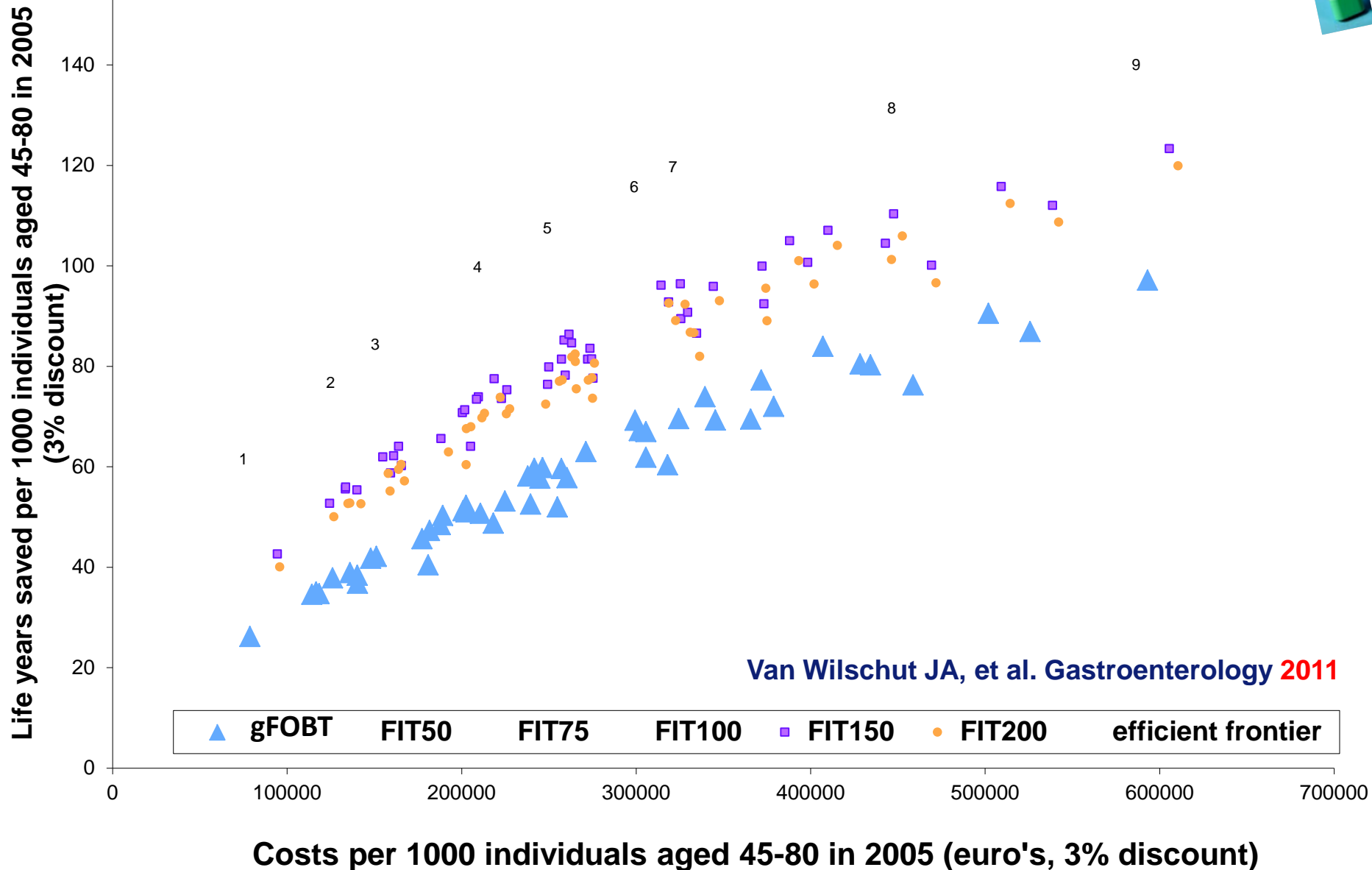


# Economic modelling of gFOBt and FIT








# Economic modelling of gFOBt and FIT



# Economic modelling of gFOBT and FIT

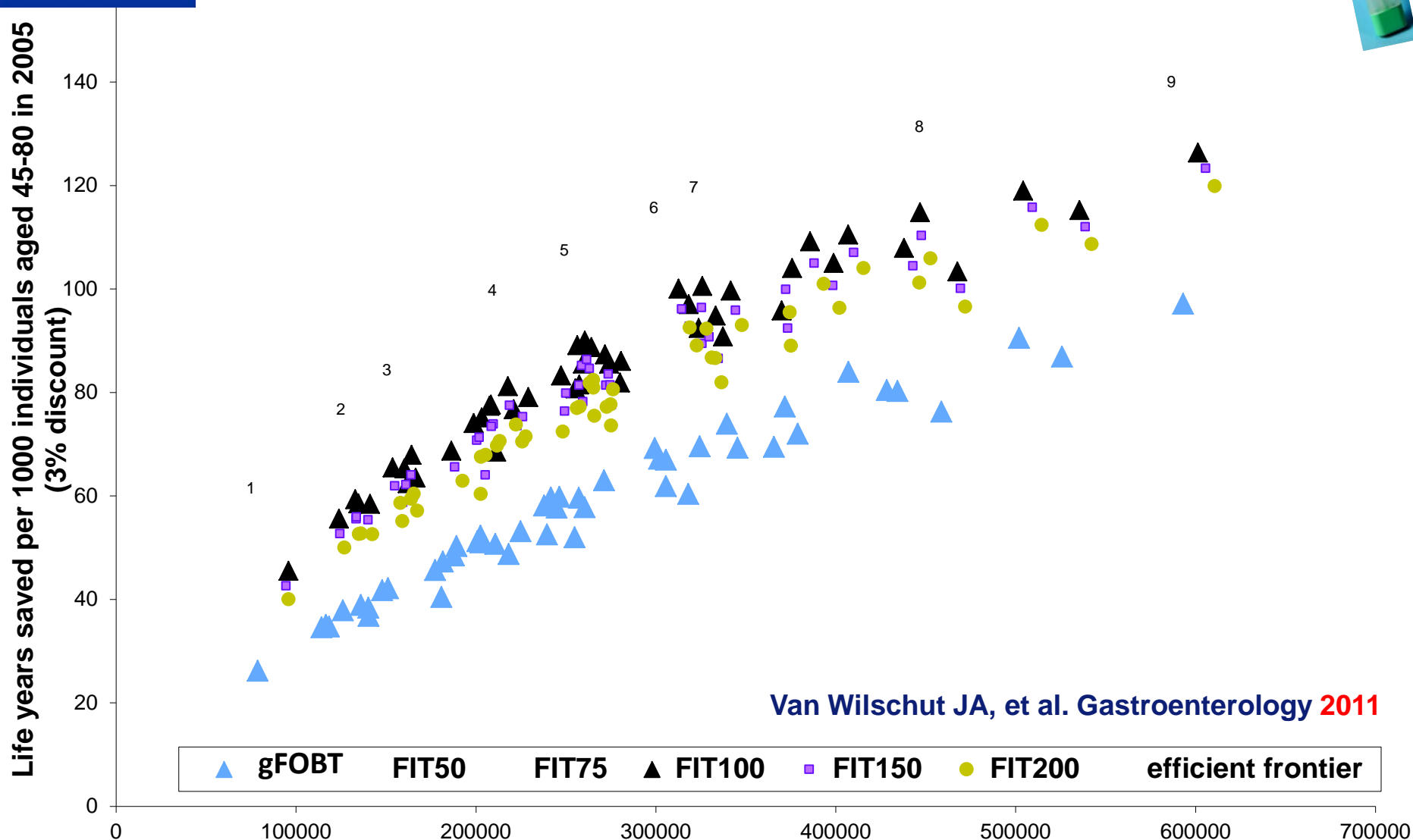


Life years saved per 1000 individuals aged 45-80 in 2005  
(3% discount)

 **gFOBT**    
  **FIT50**    
  **FIT75**    
  **FIT100**    
  **FIT150**    
  **FIT200**    
 **efficient frontier**

Costs per 1000 individuals aged 45-80 in 2005 (euro's, 3% discount)

Van Wilschut JA, et al. Gastroenterology 2011



# Economic modelling of gFOBT and FIT

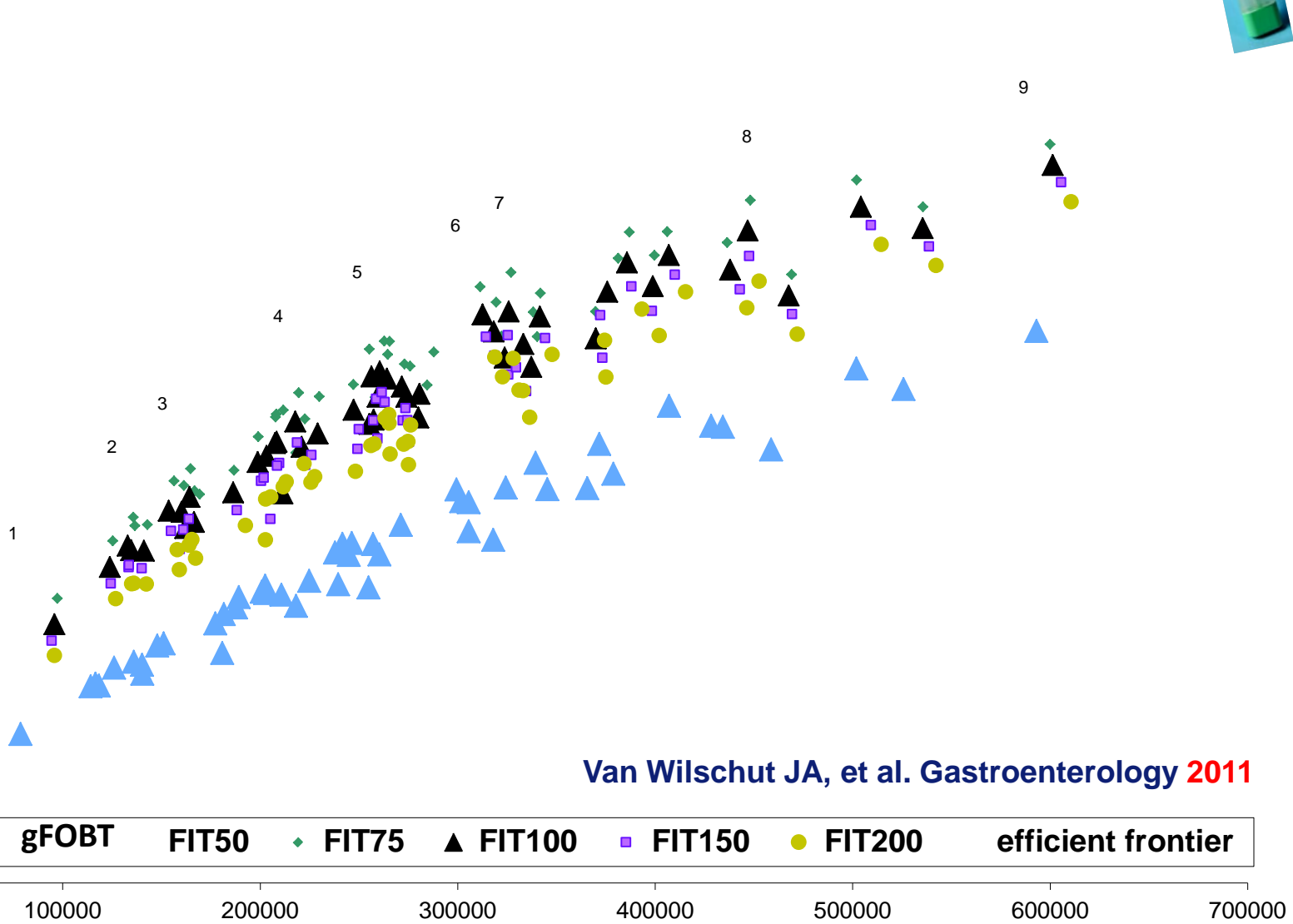


Life years saved per 1000 individuals aged 45-80 in 2005  
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▲ gFOBT   
 ▲ FIT50   
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# Economic modelling of gFOBT and FIT

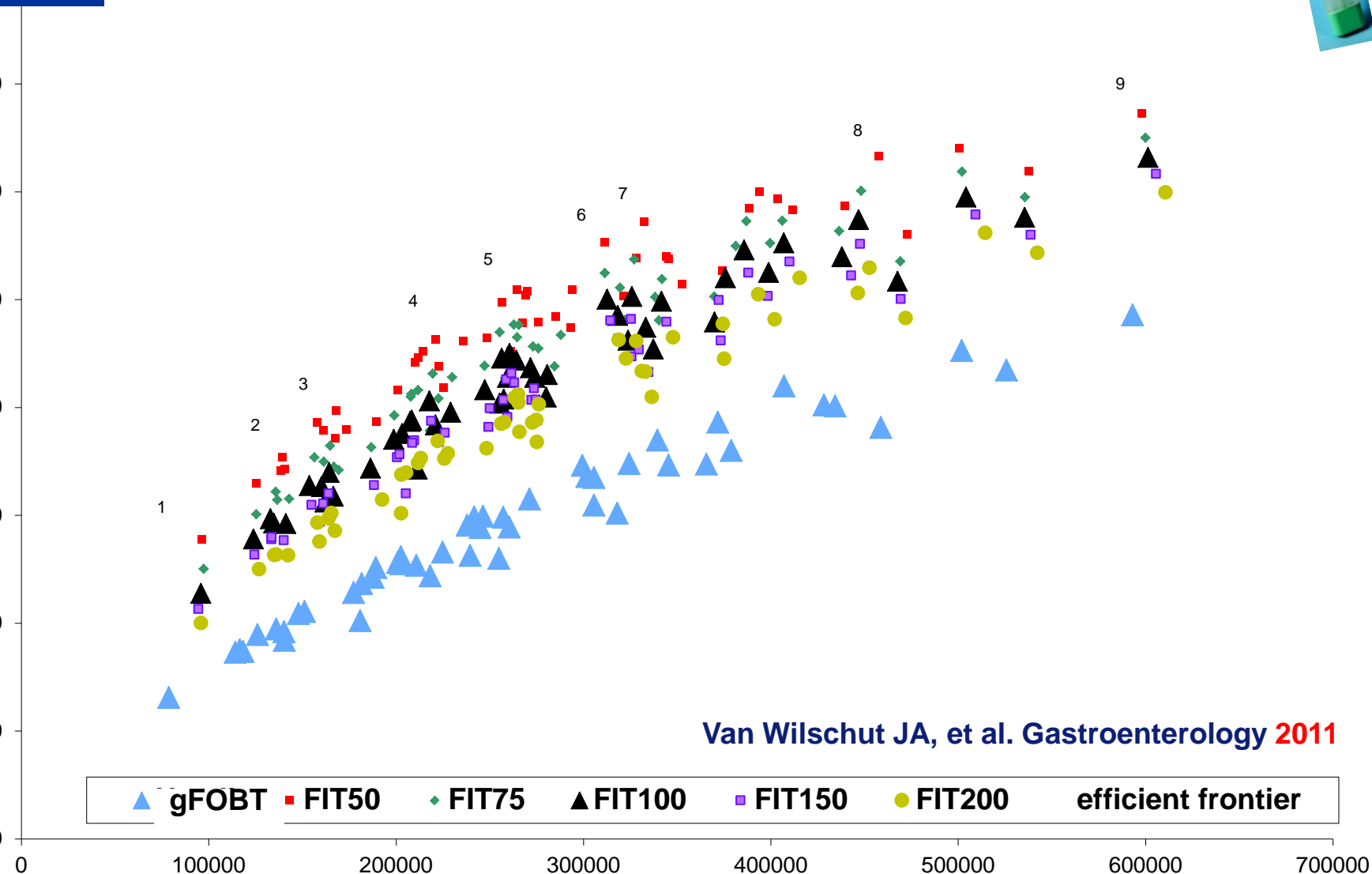


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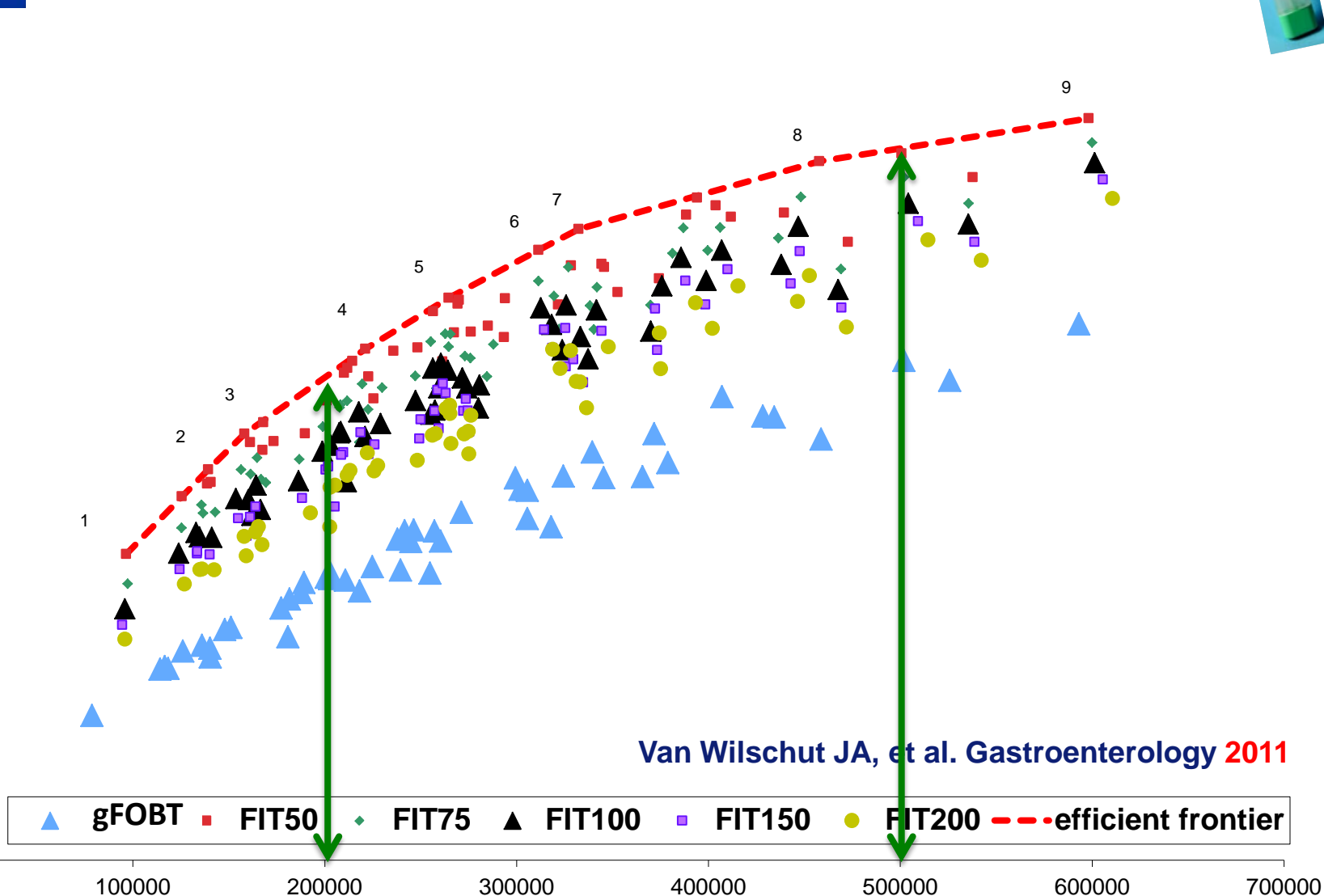




# Economic modelling of gFOBT and FIT



Life years saved per 1000 individuals aged 45-80 in 2005 (3% discount)



Costs per 1000 individuals aged 45-80 in 2005 (euro's, 3% discount)

# FIT and NHS Bowel Cancer Screening in England

## Why a Pilot?

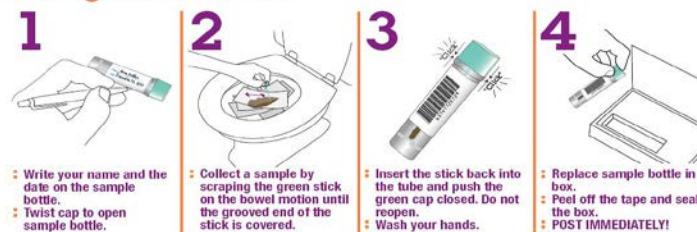
### Organisation

Write, test and refine the BCSS-FIT software  
Mailing logistics & use of barcodes

### FIT device and analysis

FIT design of packaging  
Literature inc. instructions  
Testing analytical systems

Using the test kit:



### Performance in pre-screened pop'n (resource implications)

**Uptake** – how much will it increase (SES gradient)?

**Positivity** – is it the same or different to other studies?

**Outcome** – is it similar to other studies?

### Cost

Economic assessment

Financial implications of change - gFOBT to FIT

