**Dete...ng an appropriate cut-off level ...ational screening program**
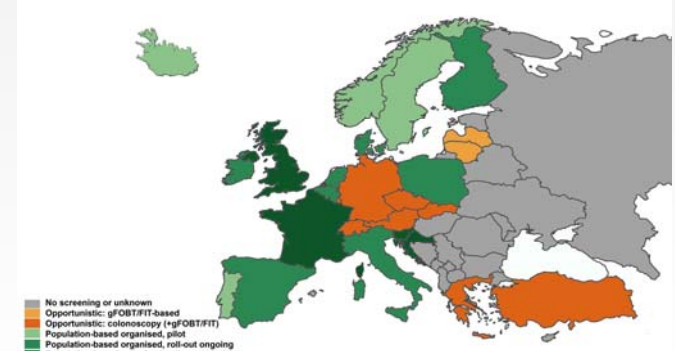
Ernst J. Kuipers
Erasmus MC, Rotterdam, NL

## Possible conflicts of interest

- None

Ernst J. Kuipers

## Colorectal cancer screening is rapidly expanding



No screening or unknown
Opportunistic: gFOBT/FIT-based
Opportunistic: colonoscopy (+gFOBT/FIT)
Population-based organised, pilot
Population-based organised, roll-out ongoing
Population-based organised, roll-out complete

Schreuders E et al. Gut 2015; in press

## Range of FIT cut-offs used in different programs

| Country | Cut-off (µg Hb/g ) |
|---|---|
| Netherlands (pilots) | 10 |
| Belgium, Spain, New Zealand | 15 |
| British Columbia*, Chile, Denmark, England, Italy, Saskatchewan, Uruguay | 20 |
| France, Martinique | 30 |
| Thailand | 40 |
| Ireland | 45 |
| Netherlands | 47 |
| Slovenia* | 67 |
| Scotland | 80 |
| Nova Scotia* | 300 |

*2 tests; referral to colonoscopy if at least 1 test is positive

Schreuders E et al. Gut 2015; in press

## Numbers needed to screen and scope with gFOBT and FIT to detect one subject with advanced neoplasia

|  | NN Screen | NN Scope |
|---|---|---|
| gFOBT | 84 | 2.2 |
| FIT[10] | 31 | 2.4 |
| FIT[15] | 37 | 2.0 |
| FIT[20] | 41 | 1.9 |
| FIT[25] | 43 | 1.8 |
| FIT[30] | 43 | 1.7 |
| FIT[35] | 46 | 1.6 |
| FIT[40] | 49 | 1.6 |

Hol L et al. Br J Cancer 2009

## Positivity rates at different cut-offs
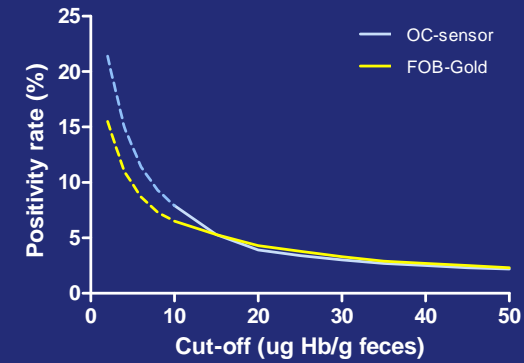


Grobbee E et al. DDW2015

## What determines an appropriate cut-off level?

- Selection of specific cut-off does not influence:
  - uptake of screening
  - numbers of FIT tests, lab activities, costs of primary screening, etc

- Increase of cut-off is associated with:
  - lower colonoscopy demand
  - higher PPV; i.e. lower number-needed-to-scope to detect advanced neoplasia

- This comes at a price:
  - higher miss rate of advanced neoplasia
  - potentially the need for a shorter screening interval

## Two ends of the rope of FIT screening

I can not do more colonoscopies. With that limitation, I want to detect as many cancers as possible

I do not mind more colonoscopies, and want to detect all cancers and as many advanced adenomas as possible with FIT

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Legend: ■ No AN ■ AN

FIT40 / FIT10

FIT10: +373% (No AN), +59% (AN)
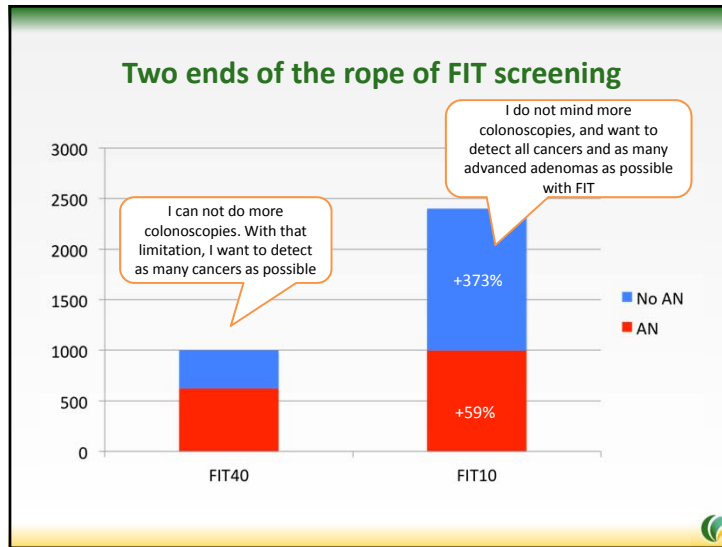
## The easy equation of a start-up FIT program

$$\text{Acceptable FIT positivity rate} = \frac{\text{colonoscopy capacity}}{\text{target population} \times \text{screening uptake} / \text{screening interval}}$$

For example:
- Colonoscopy capacity is 2000 / year
- Target population of 100,000 people
- Screening uptake (participation) = 60%
- Screening interval is 2 years

➢ Acceptable FIT positivity rate = 2000 / [(100,000 x 0.6) / 2]
= 2000 / (60,000 / 2) = 2000 / 30,000 = 6.6%

## FIT positivity and detection rates in the Netherlands

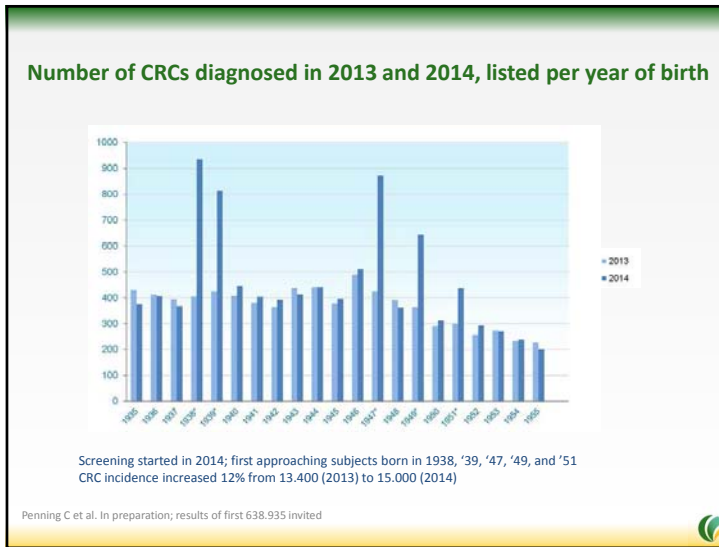|  | Pilots | National program 1st phase cut-off 15 µg Hb/g |
|---|---|---|
| Participation (%) | 50 - 62 | 68 |
| FIT positivity (%) | 6.4 | 12.0 |
| Detection of CRC* | 4.5 | 5.9 |
| Detection of AN* | 28.3 | 36.2 |
| PPV for CRC (%) | 8.2 | 6.7 |
| PPV for AN (%) | 51.6 | 40.2 |
| NN Scope for AN | 1.8 | 2.5 |

*N per 1000 screened

Penning C et al. In preparation; results of first 638.935 invited

## FIT positivity and detection rates in the Netherlands

|  | Pilots | National program 1st phase cut-off 15 µg Hb/g | National program 2nd phase Cut-off 47 µg Hb/g |
|---|---|---|---|
| Participation (%) | 50 - 62 | 68 | 72 |
| FIT positivity (%) | 6.4 | 12.0 | 7.2 |
| Detection of CRC* | 4.5 | 5.9 | 5.0 |
| Detection of AN* | 28.3 | 36.2 | 25.4 |
| PPV for CRC (%) | 8.2 | 6.7 | 9.5 |
| PPV for AN (%) | 51.6 | 40.2 | 48.1 |
| NN Scope for AN | 1.8 | 2.5 | 2.1 |

*N per 1000 screened

Penning C et al. In preparation; results of first 638.935 invited

## Number of CRCs diagnosed in 2013 and 2014, listed per year of birth



Screening started in 2014; first approaching subjects born in 1938, '39, '47, '49, and '51
CRC incidence increased 12% from 13.400 (2013) to 15.000 (2014)

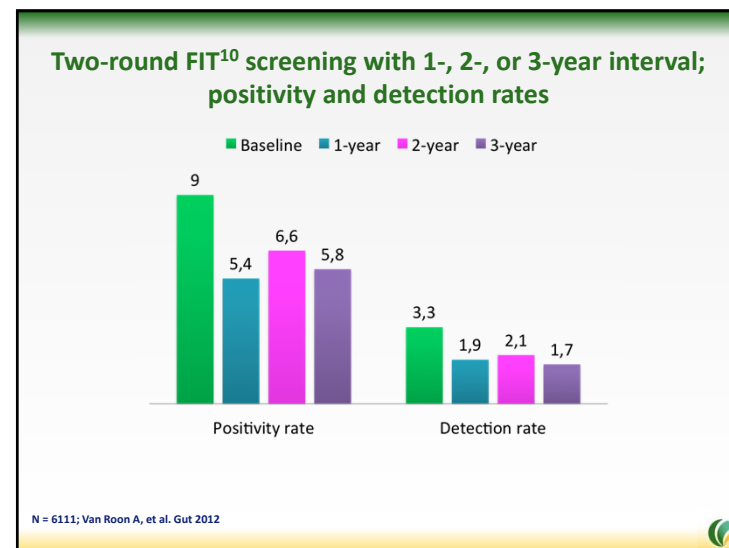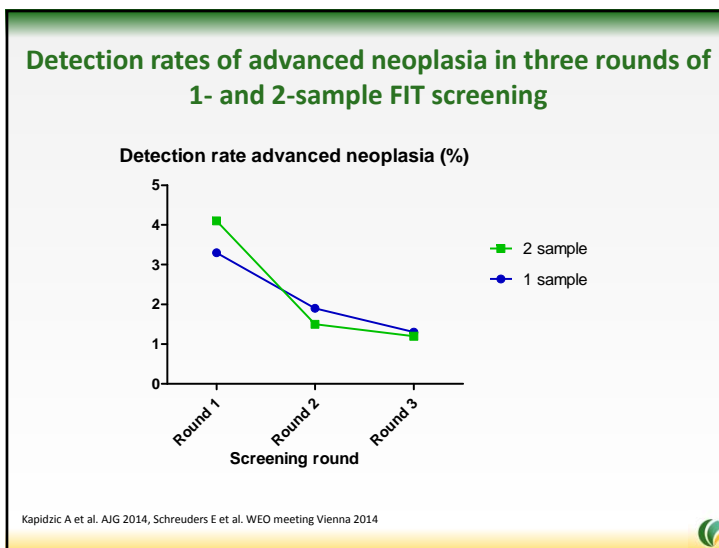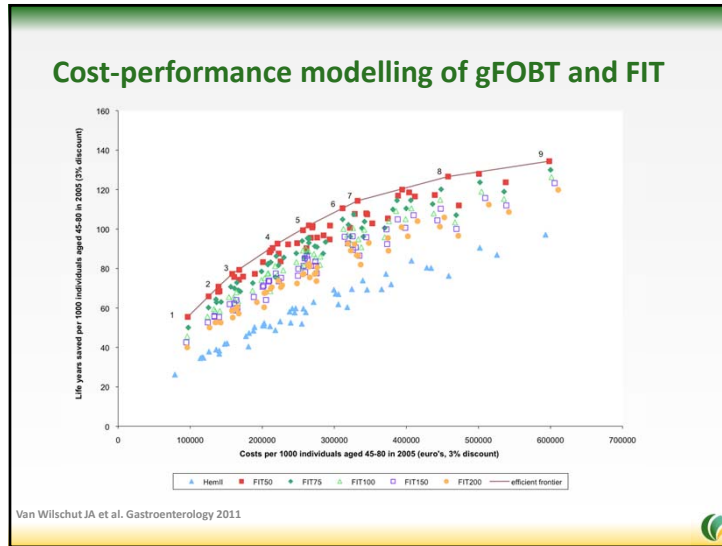Penning C et al. In preparation; results of first 638.935 invited

## The easy equation of a start-up FIT program

Acceptable FIT positivity rate = $\dfrac{\text{colonoscopy capacity}}{\text{target population x screening uptake / screening interval}}$

But:
- 1st round cut-off influences the positivity rate and yield during repeat rounds
- This may affect the optimal screening interval (and age range)

## Detection rates of advanced neoplasia in three rounds of 1- and 2-sample FIT screening



Kapidzic A et al. AJG 2014, Schreuders E et al. WEO meeting Vienna 2014

## Two-round FIT[10] screening with 1-, 2-, or 3-year interval; positivity and detection rates



N = 6111; Van Roon A, et al. Gut 2012

## Cost-performance modelling of gFOBT and FIT



Van Wilschut JA et al. Gastroenterology 2011

## Conclusions

- There is no universal optimal cut-off for any given situation

- For cut-off selection, there are two distinct phases in a screening program:
  - initial roll-out
  - steady state

- During the roll-out phase, the appropriate cut-off is primarily determined by
  - size of the target population
  - participation rate
  - colonoscopy capacity
  - screening interval

## Conclusions

- Modeling data and pilot studies suggest that the most efficient approach during the steady state phase of a screening program is:
  - use of a low cut-off
  - adjustment of screening interval

- Future studies have to demonstrate whether this can be further optimized, such as by:
  - adjustment of the target age range
  - initial 2-FIT screening at low cut-off

## The rope of FIT screening



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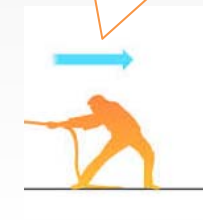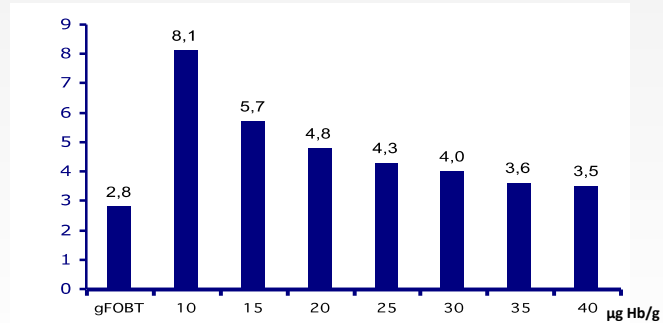
## Colorectal cancer screening is rapidly expanding

- 24 of 28 EU countries offer CRC screening
  - 13 population-based organized programs
  - 8 opportunistic programs
  - 3 piloting / planning phase

- Worldwide 20 countries have FIT based program,
  - 13 nationwide (11 rolling out, 2 complete)
  - 2 pilots
  - 5 opportunistic

Schreuders E et al. Gut 2015; in press

## Positivity rates of 1st round gFOBT and FIT screening



Hol L et al. Br J Cancer 2009