Quality assurance with FIT: from subject performance to program implementation

Graeme P Young
AM FTSE FAHMS AGAF FGESA, MB BS MD FRACP
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Flinders University

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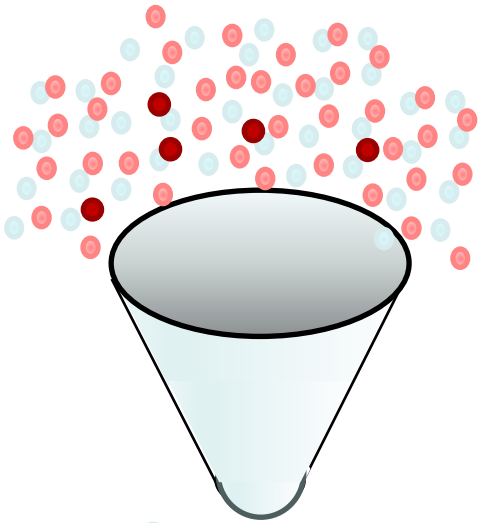
The three quality phases for FIT

- In two-step screening,… there are three sequential phases, each of which has its own quality considerations:
  - Preanalytical
  - Analytical
  - Postanalytical

- The FIT result and how it is configured is crucial as it identifies who undergoes follow-up colonoscopy.

The multi-step screening pathway



Population Tested

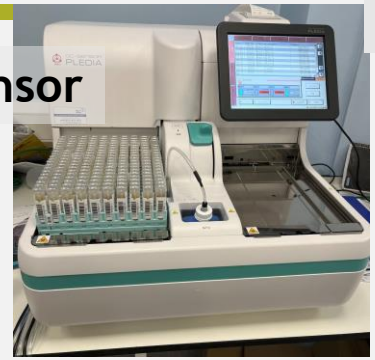
People positive

Neoplasms found

The global FIT scene comes down to 5 tests

- The WEO CRC SC EWG identified 47 different FIT systems available on the market, comprising qualitative and quantitative formats
  [Benton SC et al Clin Chim Acta 2021;517:60]
- The five most used in population-based screening are automated, analyser systems used in high throughput laboratories.
- All five are quantitative, although this is an off-label use in one.

OC-Sensor



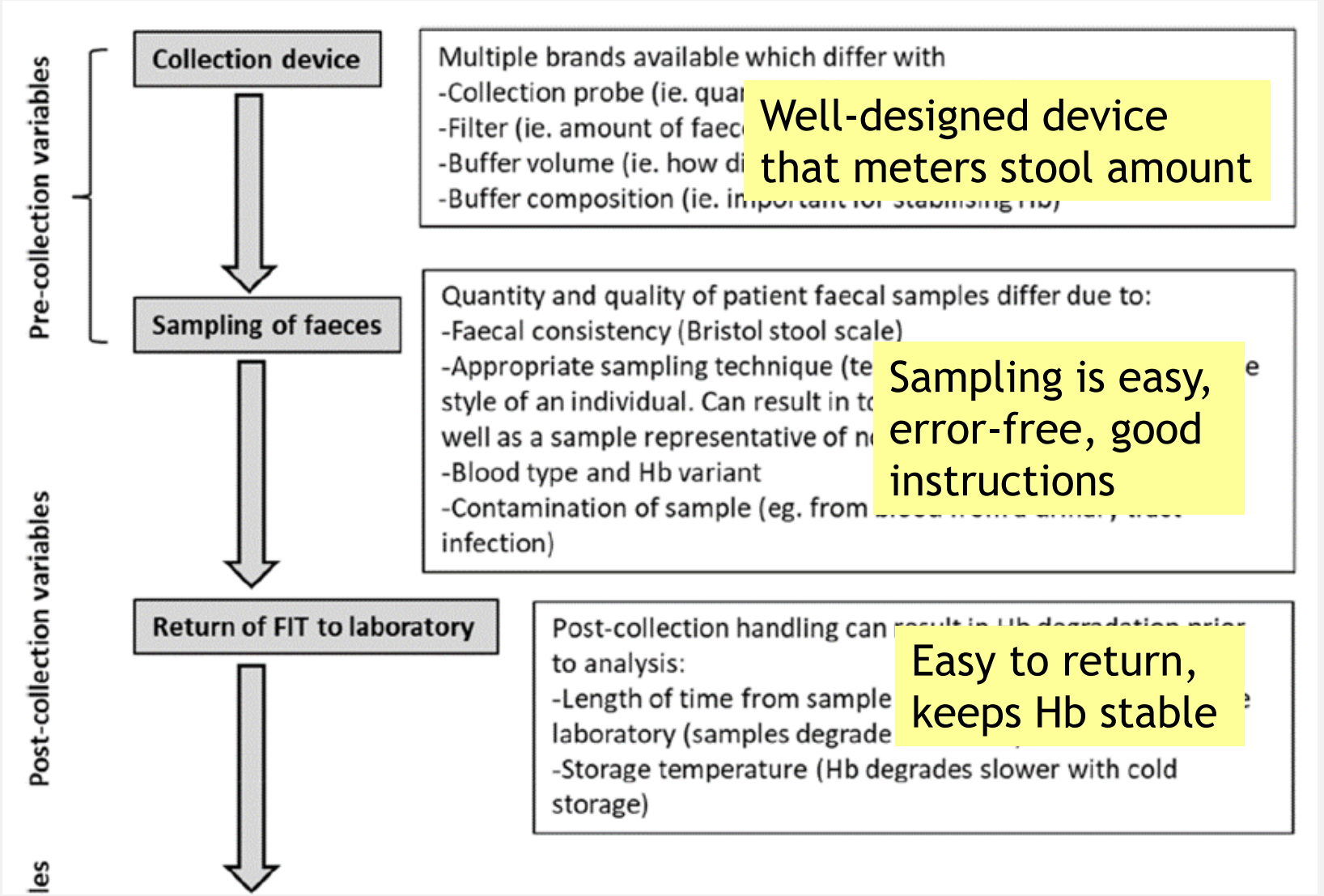
***Alfresa* - NS-Prime**

FOB Gold - SENTiFIT

Polymedco - Somagen

Preanalytical Phase – key considerations

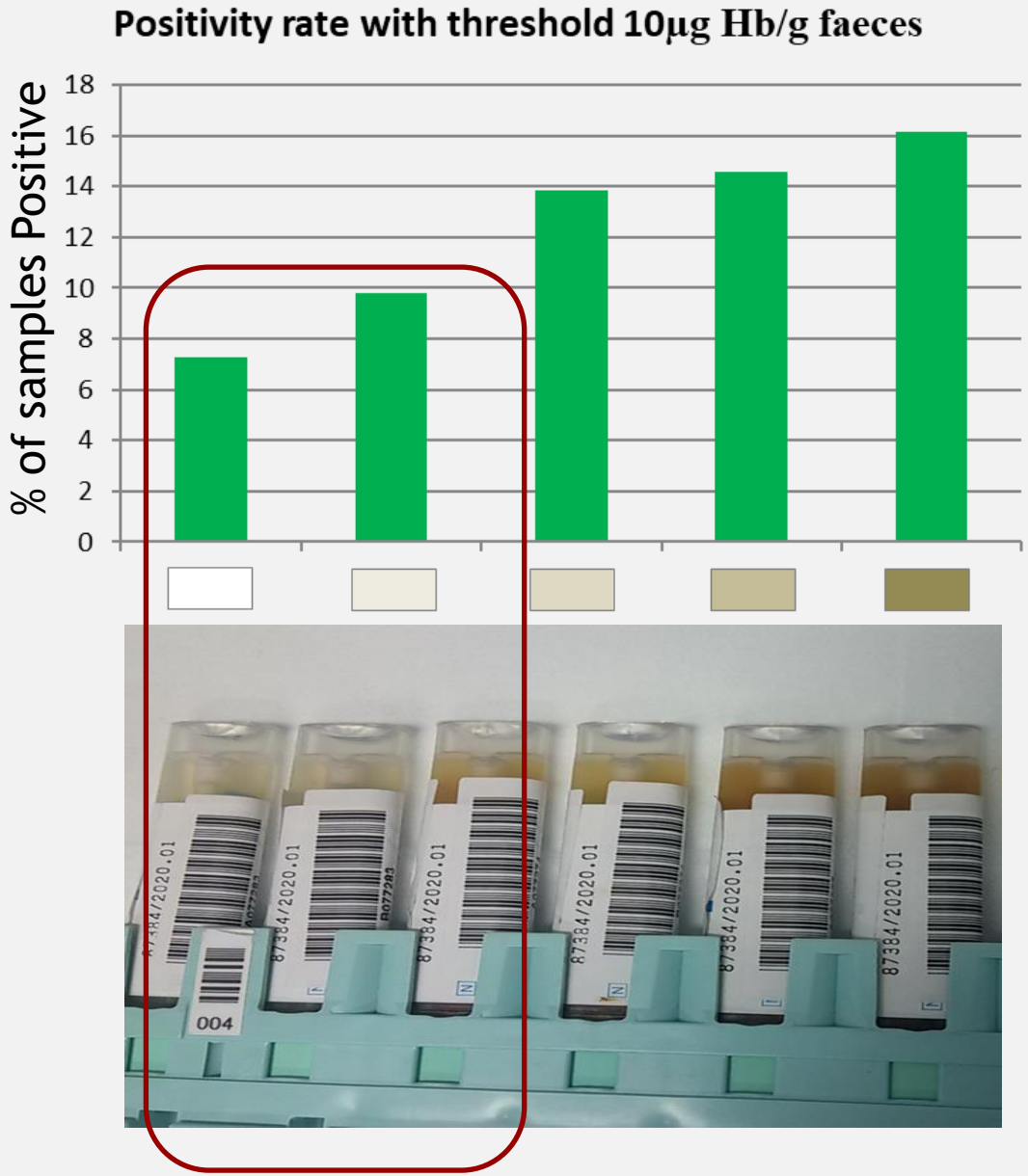
- Major quality measures:
  - **participation rate** (timely return of correctly sampled stool), and
  - **test failures** (received samples unsuitable for analysis)
  - [Benton SC et al, Clin Chim Acta 2021;517:60
- Without correct participation and return, detection by FIT will fail.



Preanalytical Phase Variables

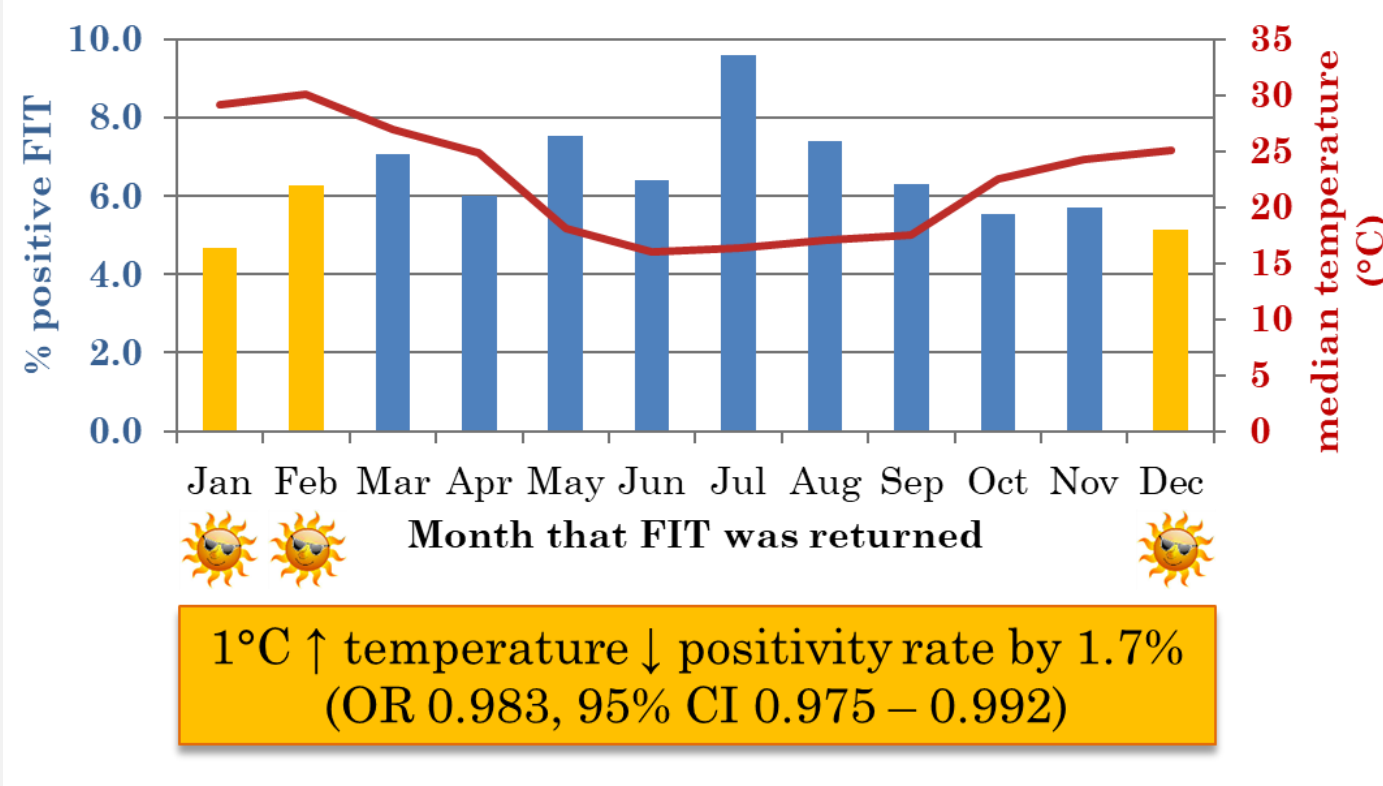
- Trials show that FIT-dependent participation rates can depend on:
  - Sampling condition/method
  - Adequacy of instructions

- Following proper sampling procedure is crucial
- Symonds EL, et al, *Canc Epidemiol, Biomarkers & Prevention* 2021; 30:175.



Hb stability is crucial to accuracy

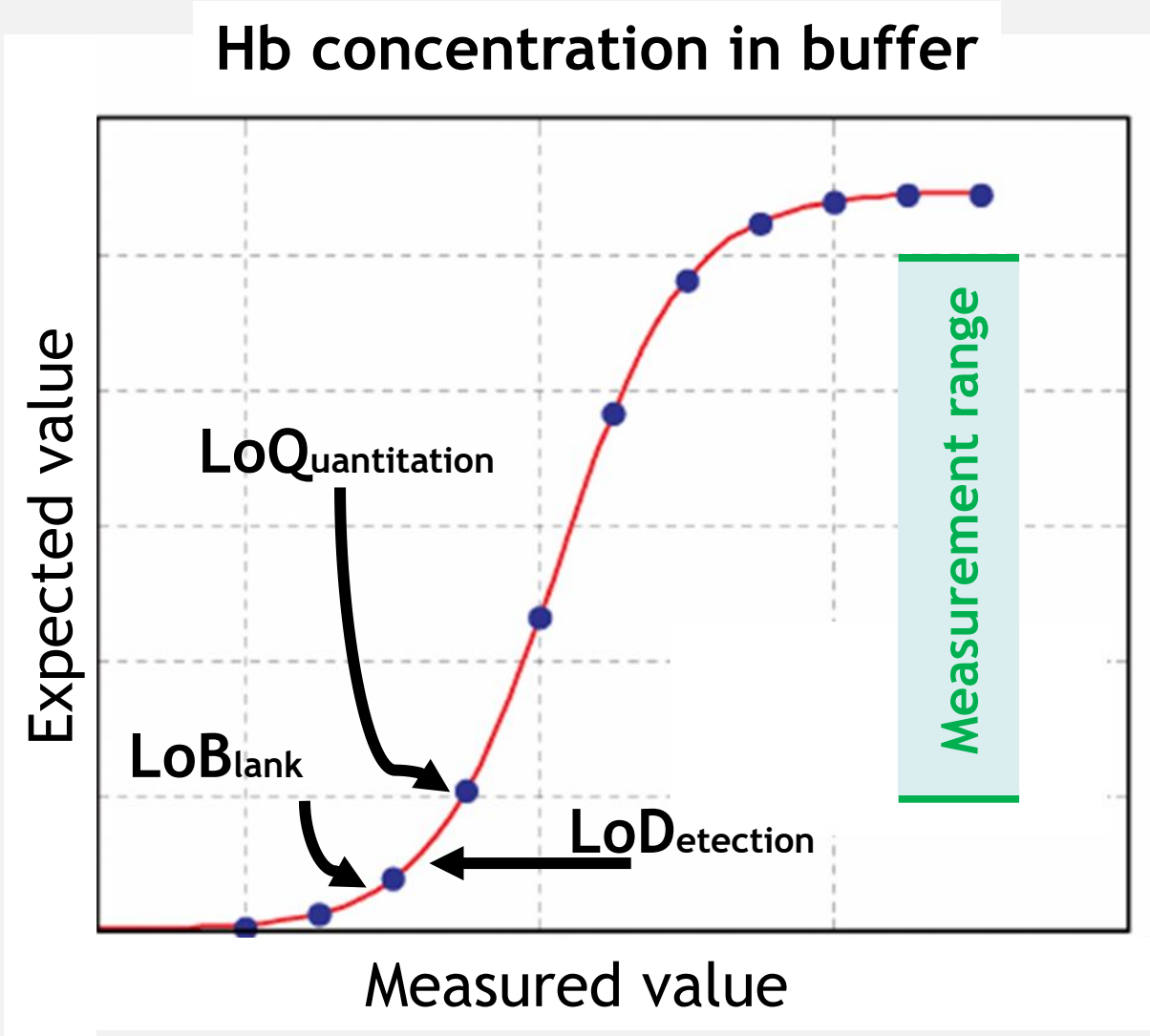
- Hb is subject to degradation and buffers vary in their ability to maintain stability.
  - Positivity rates can be lowest in higher temperature months
  - Colorectal neoplasms are missed if higher temperatures cause the measured f-Hb to fall below the positivity threshold.
- Timely return, in a stable buffer, is crucial.



- Symonds EL, et al. Journal of Medical Screening, 2015;22:187-93.

Analytical Phase – laboratory standards

- Quality requires the following:
  - Precision and Trueness
  - Linearity (measurement range)
  - Detection limits (of quantitation, of detection, of blank)
  - Consistency across instruments and time (ongoing monitoring)
- Recent WEO guidelines …: **"the analytical performance … of the test must be formally documented according to relevant standards, such as … the international Clinical and Laboratory Standards Institute (CLSI) or the Quality System Requirements (QSR) of the USA."**



The ideal FIT for PBOS programs

1. Laboratory receipt of participant sample with automated **reliable reading of participant identity**
2. High capacity **automated sampling** from the device, and automated analytical **assay**.
3. It must provide **accurate, reliable and reproducible results** under conditions of widespread use.
4. **Quality control** and assessment system applied and reviewed regularly including **external EQAS**.
5. A policy for **repeat sample** collection if the sample provided is unsatisfactory.
6. **Reporting of the result in a manner applicable to the program.**
   - If Qualitative, use the program's positivity threshold

The chosen positivity threshold is crucial to achieving a program's goals.

Moving forward from the Analytical phase

1. Analysers determine the Hb concentration in the device buffer.
2. The result is dependent on:
   - amount of faeces collected and
   - the buffer volume;

3. That reported f-Hb is not readily transferred between tests – it is valid only for that system.
4. **There is no international reference standard material for this purpose.**

- The FIT EWG recommended harmonization by converting units of concentration as follows:
  - FROM ng Hb/ml buffer,
  - TO mcg Hb/g feces.
- This is achieved by correcting for the amount of stool collected and its dilution in the buffer.
- Will it give equal **clinical** accuracy at an equal positivity threshold?
- Studies in Taiwan and Germany show that some variation remains.

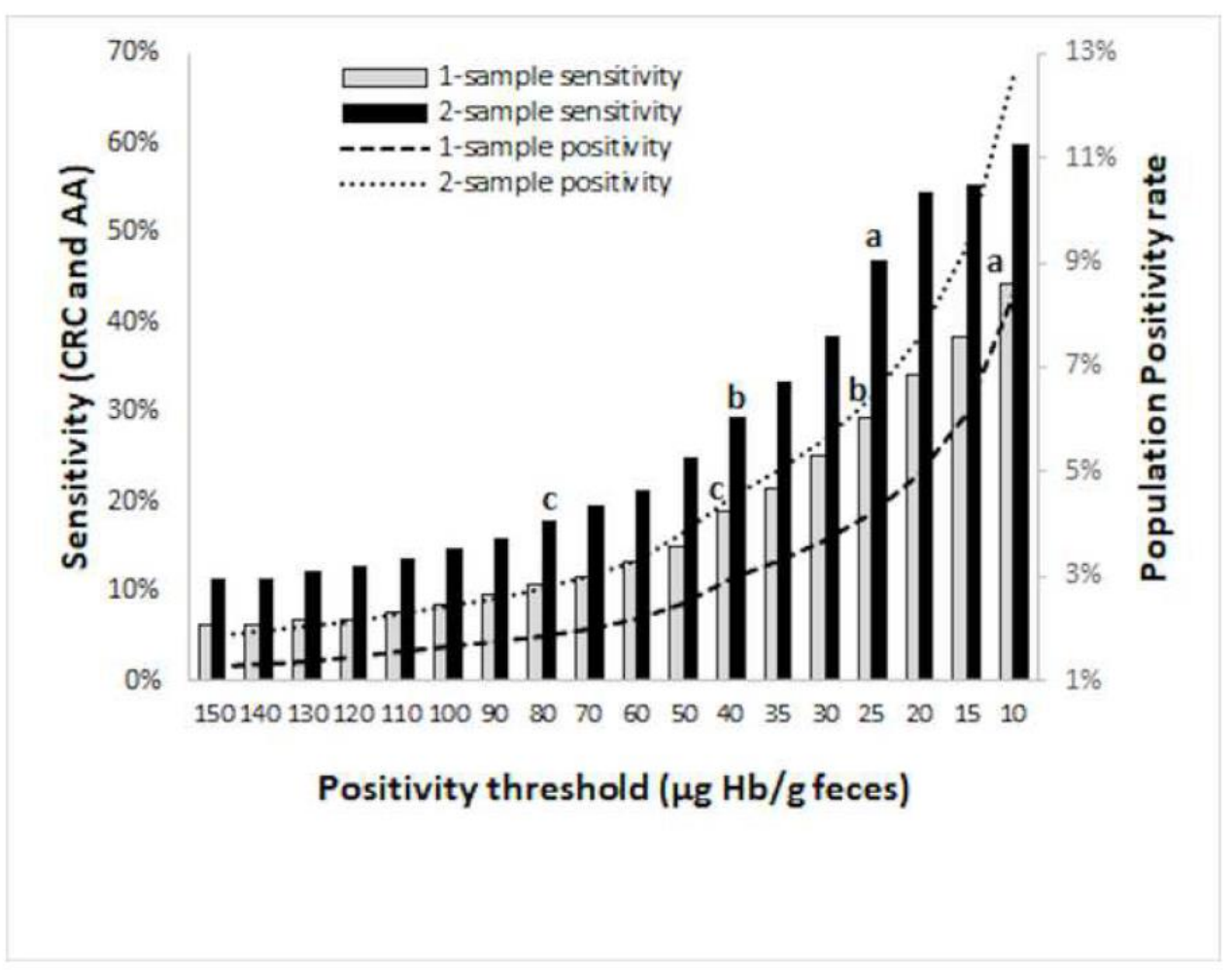
Regulatory frameworks and marketing

- **Just because a test gets formal documentation of analytic quality, it does not ensure that it will meet program goals.**
- **Regulatory frameworks** address a test's utility (accuracy) when used according to a stipulated positivity threshold.
- "*Regulatory bodies (FDA, EU, etc.) provide a framework for judging a test's utility based on manufacturer's documented studies on accuracy.*"
  - *"Require a disclaimer about the consequences of a test's imprecision.*
- "***Marketing programs** typically expound on the results of closely monitored, controlled clinical trials that report test accuracy against a set positivity threshold*" in a particular study context.
- To report accuracy the threshold for positivity (*pre- or post-hoc*) is chosen by those reporting the results.
- Just because regulatory frameworks and clinical studies document test accuracy at a given threshold, *it does not ensure that it will meet a program's goals **at that positivity threshold**.*

Fitting the FIT to program goals

- Major considerations are:
  - **Workload:** Efficiency of detection of CRC (mortality benefit with lower effort),
  - **Sensitivity:** Better precursor detection with higher colonoscopy effort, or
  - The **middle ground** that balances sensitivity with workloads.
- Adjusting the positivity threshold is crucial if we are to meet goals.
- It was a major recommendation of the new test evaluation EWG

- Young GP, et al. Gastroenterology, 2020;159:1561-1563.



Positivity thresholds vary globally

- A wide range of thresholds are in use as demonstrated by our recent global survey.
- Experience has shown that about one-third of programs decided to adjust the initial threshold to ensure that goals could be delivered.

Threshold (µg Hb/g)	Region
10	Switzerland
15	Israel, Norway
20	Australia, Manitoba, Italy, Catalonia
25	Finland
20/30	Taiwan
40	New Zealand, Sweden (female)
47	Netherlands
80	Scotland, Sweden (male)
120	England, Northern Ireland, Wales

Pilot studies in a population are important to test if the chosen threshold is applicable

Conclusions

- **Preanalytical:** Participation rate involving timely return of adequately sampled stool.
- **Analytical:** Adherence to relevant laboratory and regulatory standards, with ongoing accountability.
- In considering program implementation, note that initial clinical studies and stated analytical characteristics might not identify the best positivity threshold for a program.
- **Meeting program goals** requires identification of the positivity threshold that suits program goals, together with ongoing monitoring of its suitability.
- A formal pilot study addressing every quality issue in the three phases are very helpful.