Royal Surrey NHS Foundation Trust

Berkshire and Surrey Pathology Services

NHS Cancer Screening Programmes

Evaluation of new non-invasive screening tests for Colorectal Cancer

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BSPS is a joint venture between: Ashford and St. Peter's Hospitals NHS Foundation Trust; Frimley Health NHS Foundation Trust; Royal Berkshire NHS Foundation Trust; Royal Surrey NHS Foundation Trust and Surrey and Sussex Healthcare NHS Trust

Legal entity host: Frimley Health NHS Foundation Trust

Background

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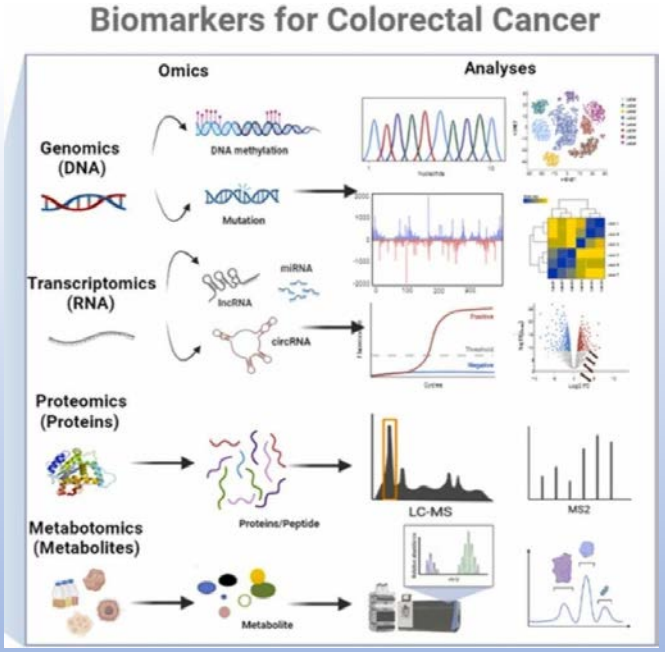
NHS Cancer Screening Programmes

- New non-invasive screening tests for CRC are rapidly emerging
  - novel biomarkers
  - different sample types
  - risk stratification approaches



Background

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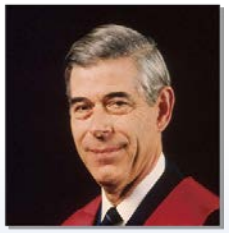
NHS Cancer Screening Programmes

- Conducting trials with mortality reduction as the end point is challenging and takes a long time
- Need to be able to rapidly evaluate new screening tests to support implementation

Randomised Controlled Trials of mass screening using FOBt

- *UK Nottingham*
- *USA*
- *Denmark*
- *Sweden*



Meta analysis of biennial screening
(follow-up 11 - 18 years) *Towler et al 1998*
- *15% reduction*

WEO
World Endoscopy Organization

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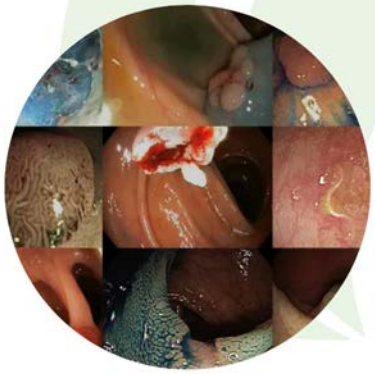
Committees

- Artificial Intelligence, Ad hoc Committee
- Award, Ad hoc Committee
- Colorectal Cancer Screening Committee
- Education Committee
- Esophageal Diseases, Ad hoc Committee
- Executive Committee
- Inflammatory Bowel Disease, Ad hoc Committee
- Documentation & Standardization Committee
- Outreach, Ad hoc Committee
- Pancreato-biliary, Ad hoc Committee
- Research Committee
- Standards of Practice & Publications (SPP) Committee
- Stomach and Duodenal Diseases Committee
- Super Minimally Invasive Interventions, Ad hoc Committee

CRC Screening Committee



The WEO Colorectal Cancer (CRC) Screening Committee focuses on the science and practice of colorectal cancer screening.

Expert Working Groups

The Expert Working Groups (EWGs) of the Colorectal Cancer (CRC) Screening Committee were created to cover certain elements of CRC screening that required more in depth discussions. To date, there are 7 EWGs. Click on the name to learn more about each of them:

- Evaluation of New Tests (to be updated)
- FIT for Screening
- WEO Coalition to Reduce Inequities in CRC Screening
- Polyp Detection, Characterization, Resection and AI
- PCCRC and Quality in Colonoscopy
- Surveillance after Colorectal Neoplasia

Evaluation of new Tests

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Cancer Screening Programmes

Colon

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An efficient strategy for evaluating new non-invasive screening tests for colorectal cancer: the guiding principles

Robert S Bresalier,[1] Carlo Senore,[2] Graeme P Young,[3] James Allison,[4] Robert Benamouzig,[5] Sally Benton,[6] Patrick M M Bossuyt,[7] Luis Caro,[8] Beatriz Carvalho,[9] Han-Mo Chiu,[10] Veerle M H Coupé,[11] Willemijn de Klaver,[12] Clasine Maria de Klerk,[13] Evelien Dekker,[14] Sunil Dolwani,[15] Callum G Fraser,[16] William Grady,[17] Lydia Guittet,[18] Samir Gupta,[19] Stephen P Halloran,[20] Ulrike Haug,[21] Geir Hoff,[22,23] Steven Itzkowitz,[24] Tim Kortlever,[25] Anastasios Koulaouzidis,[26] Uri Ladabaum,[27] Beatrice Lauby-Secretan,[28] Mārcis Leja,[29] Bernard Levin,[30] Theodore Robert Levin,[31] Finlay Macrae,[32] Gerrit A Meijer,[9] Joshua Melson,[33] Colm O'Morain,[34] Susan Parry,[35,36] Linda Rabeneck,[37] David F Ransohoff,[38] Roque Sáenz,[39] Hiroshi Saito,[40] Silvia Sanduleanu-Dascalescu,[41] Robert E Schoen,[42] Kevin Selby,[43] Harminder Singh,[44] Robert J C Steele,[45] Joseph J Y Sung,[46] Erin Leigh Symonds,[47] Sidney J Winawer,[48] Members of the World Endoscopy Colorectal Cancer Screening New Test Evaluation Expert Working Group

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2023-329701).

For numbered affiliations see end of article.

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ABSTRACT

Objective New screening tests for colorectal cancer (CRC) are rapidly emerging. Conducting trials with mortality reduction as the end point supporting their adoption is challenging. We re-examined the principles underlying evaluation of new non-invasive tests in view of technological developments and identification of new biomarkers.

Design A formal consensus approach involving a

missed lesions. Phases III and IV findings will provide the real-world data required to model test impact on CRC mortality and incidence.

Conclusion New non-invasive tests can be efficiently evaluated by a rigorous phased comparative approach, generating data from unbiased populations that inform predictions of their health impact.

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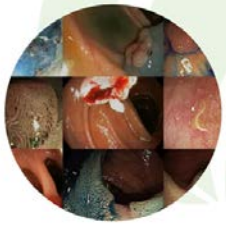
World Endoscopy Organization

CRC Screening Committee



The WEO Colorectal Cancer (CRC) Screening Committee focuses on the science and practice of colorectal cancer screening.

Bresalier RS et al. Gut; 72: 1904-1918. doi:10. 1136/gutjnl-2023-329701

Authors

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- Membership consisted of experts from around the globe with knowledge and experience in practice or research relevant to CRC screening
  - Gastroenterologists, epidemiologists, GI surgeons, Clinical biochemists, public health physicians, tumour biologists

Aim

Colon

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An efficient strategy for evaluating new non-invasive screening tests for colorectal cancer: the guiding principles

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- To provide an efficient , feasible and rigorous approach to evaluate emerging new non-invasive tests for use in the two main colorectal screening contexts (population based screening programmes and structured opportunistic screening)

- CRC mortality as the end point is challenging due to large study size required, time involved and cost.

Method

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- Consensus process based on Glaser and Delphi approaches
- 12 specific questions (“principles”) drafted and circulated. These were re-drafted further to email discussions, teams meetings and commenting from whole group.
- Each member agreed/ disagreed with each principle on a 5 point scale
- Principles accepted >80% agreement reached (4 rounds of voting)

The 12 Principles

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NHS Cancer Screening Programmes

Original research

Table 1 The topics addressed in each of the principles established by the consensus process

Principle number	Topic
1	Desired outcome of CRC screening.
2	Screening is a multistep process.
3	A screening test identifies individuals with an increased likelihood of CRC and/or advanced precursor lesions.
4	Nature of precursor lesions most important to detect.
5	New biomarkers might detect lesions with a different natural history.
6	Outcomes to be estimated in a screening population.
7	Expectations of a new non-invasive test.
8	An adjustable test positivity threshold accommodates different programme goals.
9	Predicting value by paired comparison with a proven non-invasive screening test.
10	Evaluation proceeds through increasingly complex phases.
11	Accuracy required for evaluation in a screening population.
12	Analytical specifications, standards and performance.

- "Screening for CRC aims to reduce CRC mortality and/ or incidence by detecting readily treatable CRC and advanced precursor lesions without adversely affecting the health status or overly burdening those who participate in screening"

- Population based organised screening programmes (PBOS) preferred – provide greater protection against harms of screening eg over-testing, poor quality, poor follow up

- Structured opportunistic screening (SOS) also exists in some countries eg USA

Principle 2: Screening is a multistep process

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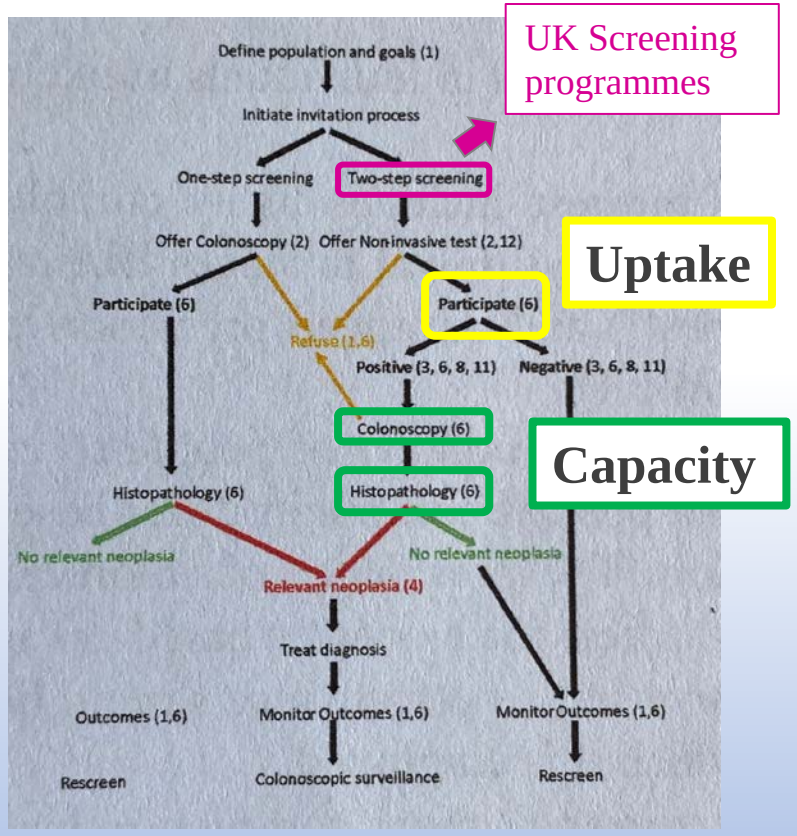

Figure 1 The multistep screening pathway characteristic of organised screening programmes and demonstrating the one-step and two-step strategies[3] as discussed in principle 2. How the principles relate to steps and outcomes are identified by the numbers in parentheses. Colours identify important outcomes relevant to detection.

- The screening test is just one event in a complex process
- All aspects of the process need to be considered before implementing any changes

Principle 3: A Screening test identifies individuals with an increased likelihood of CRC and/ or advanced precursor lesions

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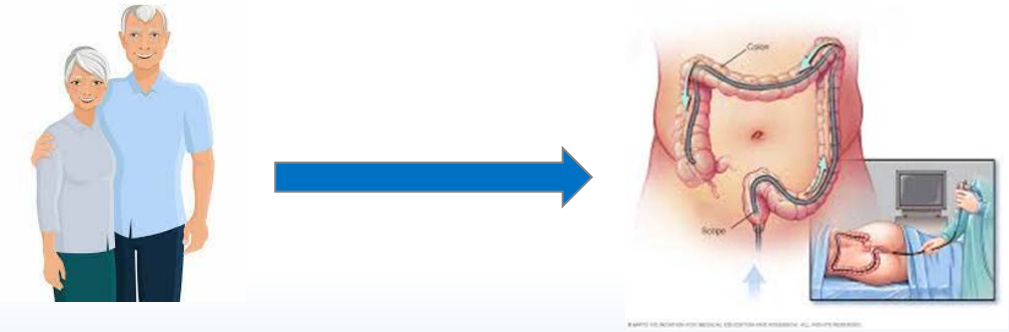
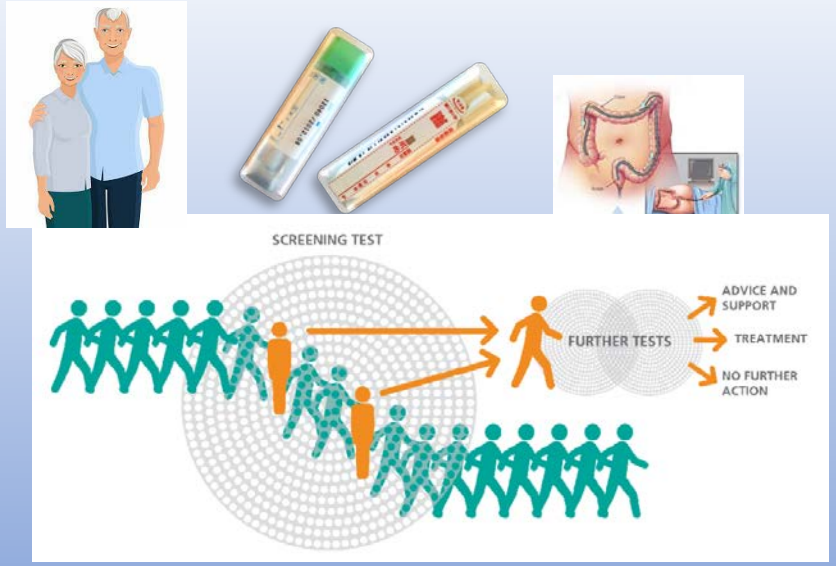
1-step screening



2-step screening



Principle 4: Nature of precursor lesions most important to detect

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- Advanced Adenomas and Advanced Serrated Lesions – most important
- Screening test that identifies these precursor lesions is likely to reduce CRC incidence
- **Challenging:** at the early stage patients often asymptomatic so there is limited data on morphological features of these lesions
- More research needed to establish characteristics that objectively identify those characteristics of the lesions that are most important to detect in screening – useful characteristics could then be used as molecular biomarkers
- Sensitivity of FIT is limited
- Tests that incorporate neoplasia derived DNA alongside f-Hb most sensitive

Principle 5: New biomarkers might detect lesions with a different natural history

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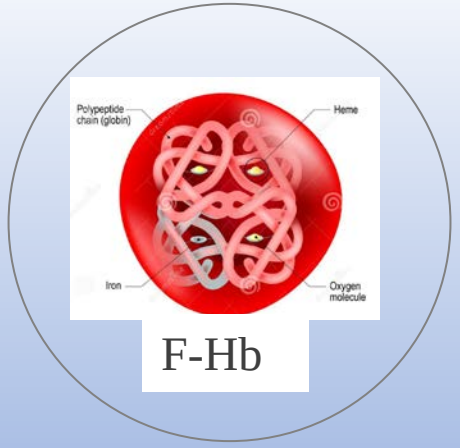
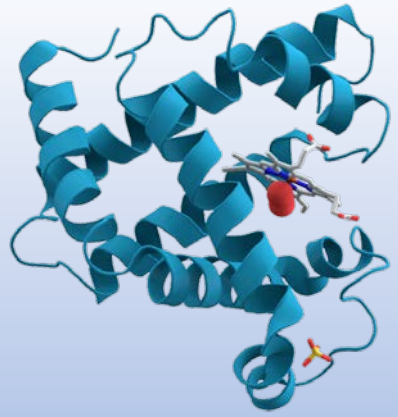
- Important to explore concordance between the new and comparator test results to identify if differences in neoplasia related biology should be considered, especially for pre-cursor lesions



F-Hb



Principle 6: Outcomes to be estimated in a screening population

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- **New test application at key points along a multistep screening pathway should be assessed at key points in the intended use population**

- Value of a non-invasive test is determined by how well it detects CRC and advance precursors AND how well it improves elements of the screening pathway that are dependent on the test
  - Participation (uptake)
  - Laboratory considerations
  - Detection rate/ stage shift

- Over-diagnosis and PPV important to consider

Principle 7: Expectations of a new non-invasive test

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- **The effectiveness of a new test may be predicted when compared with a standard (comparator or index test) where the comparator's effectiveness has been previously demonstrated**

- FIT is a suitable standard by which to judge a new non-invasive screening test in the context of organised two step population screening,
- The FIT selected must be one with well-established diagnostic accuracy supported by large reference data sets from screening practice

- No consensus on what constitutes an adequate diagnostic sensitivity
- It should be at least as good, if not better than FIT at a low f-Hb threshold

Principle 8: An adjustable test positivity threshold accommodates different programme goals

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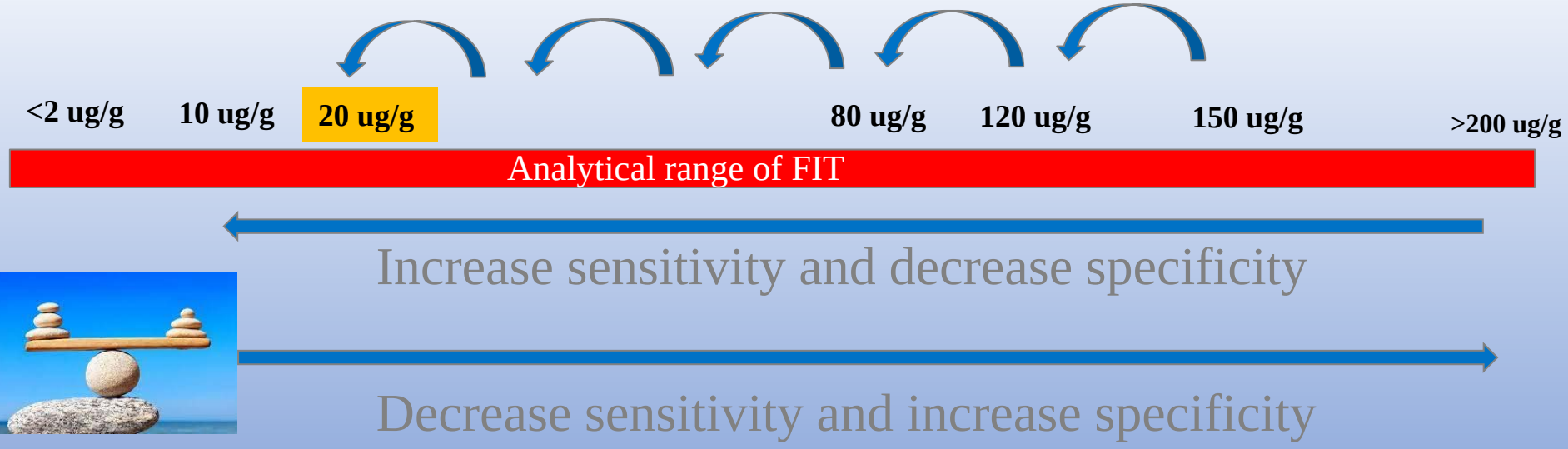
- An adjustable positivity threshold or algorithm enables the choice of test accuracy parameters (diagnostic sensitivity and specificity) and test positivity rate that best match desired goals of a screening programme

Can we add anything to improve sensitivity and specificity?



Principle 8: An adjustable test positivity threshold accommodates different programme goals

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Qualitative tests for faecal occult blood

- gFOBt
- FIT – lateral flow methods

Detect very low concentrations of f-Hb

Qualitative FOB product	Manufacturer LOD µg/g	Mean OC-Sensor Hb µg/g (each sample n=3)																
		0	0	1	2	3	4	5	6	6	7	7	8	10	20	27	82	82
		Results from qualitative FIT products																
Actim Fecal Blood	25	0	Fail*	0	0	0	0	0	0	100	0	100	100	100	100	100	100	100
Colonview Colonview reader	Not quoted	0	0	100	0	0	100	100	50	100	0	100	100	100	100	100	100	100
		**						100	0		*	100	**		100	**		
Diaquick FOB Cassette	5 supplier, 6 manufacturer	0	0	100	0	0	100	0	0	100	0	100	100	100	0	100	100	100
FOB Rapid Test	6	0	0	100	0	0	100	0	0	100	0	0	100	100	100	100	100	100
Hexagon OBTI	Not quoted	0	0	100	100	0	50	0	0	100	0	100	100	100	100	100	100	100
Nadal FOB	2	0	0	100	100	0	100	50	0	100	0	100	100	100	100	100	100	100
Nadal FOB75	3.75	0	0	100	0	0	50	0	0	100	0	100	100	100	0	100	100	100
Proflow Faecal Occult Blood	5	0	0	100	0	0	50	0	0	100	0	100	100	100	100	100	100	100

Principle 9: Predicting value by paired comparison with a non-proven invasive screening test

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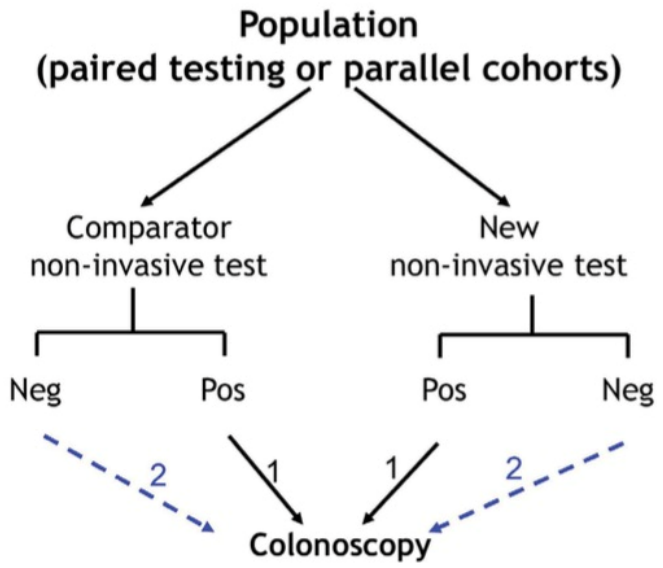

1 For comparing true-positive and false-positive fractions.
2 For comparing sensitivity and specificity (depending on biases due to population selection).

Figure 2 Diagrammatic outline of a trial design appropriate for comparing non-invasive tests in the initial phases of test evaluation. Paired testing is conducted in a single cohort where an individual does both the new and the comparator test, whereas parallel testing is where study participants are randomised to one or the other test. Neg, negative result; Pos, positive result.

Paired testing – individuals get new and comparator test

Parallel testing – individuals get either new OR comparator test

- Can assess all parts of the programme eg
  - Uptake
  - Diagnostic outcomes
  - Positivity/ referrals

Principle 9: Predicting value by paired comparison with a non-proven invasive screening test

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FIT vs gFOBT

Clinical outcomes using a faecal immunochemical test for haemoglobin as a first-line test in a national programme constrained by colonoscopy capacity

Robert JC Steele[1], Paula J McDonald[2], Jayne Digby[2], Linda Brownlee[2], Judith A Strachan[2], Gillian Libby[2], Paula L McClements[3], Janice Birrell[4], Francis A Carey[5], Robert H Diament[6], Margaret Balsitis[7] and Callum G Fraser[8]

Increased uptake and improved outcomes of bowel cancer screening with a faecal immunochemical test: results from a pilot study within the national screening programme in England

Sue Moss,[1] Christopher Mathews,[1] T J Day,[2] Steve Smith,[3] Helen E Seaman,[4] Julia Snowball,[4] Stephen P Halloran[4,5]

- Parallel testing
- Increased uptake
- More CRC and adenomas detected- thresholds lower

What plans for new tests showing promise…..?

- Risk stratification
- Microbiome
- Novel biomarkers

Principle 10: Evaluation proceeds through increasingly complex phases

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Evaluation of a new test should follow a four-phase (sequential) evaluation

Phase	Goal(s)	Context	Approach and measures	Hurdle for progression
1	**Main:** Differentiates between CRC and non-neoplastic states?	Prescreening cohorts – limited	Distribution of test results in cohorts with and without CRC	• Test result must differ significantly in cancer cases.
2	**Main:** Detects early cancer and precursor lesions? **Others:** Initial positivity threshold? Accuracy relative to comparator? Causes of false positives.	Prescreening cohorts - extensive	Distribution of test results in cohorts with CRC relevant precursor lesions, other colorectal diagnoses and no disease. Parallel or paired testing of new and comparator tests will be informative.	• Preliminary (although biased) estimates of accuracy are shown to be promising. • ROC analysis identifies a suitable positivity threshold.
3	**Main:** Test accuracy in a typical screening evaluation? Test acceptance? **Others:** Test failure rate? Other variables for modelling effectiveness and cost-effectiveness.	Screening populations – single round	Apply test prospectively to a typical unbiased intended-use population. Choose study design appropriate to program goal and jurisdictional context: e.g., colonoscope all for estimating test accuracy, parallel testing for comparing non-invasive tests and intention-to-screen outcomes.	• A significant improvement in some aspect of screening. • Non-inferior in accuracy to a comparator test, OR • Accuracy likely delivers benefit. • Feasible colonoscopy workload. • Modeled effectiveness and cost-effectiveness are satisfactory.
4	**Main:** Missed lesions or adverse events? **Others:** Participation rates over time and retest intervals?	Screening population – multiple rounds	Apply the test prospectively to an intended-use screening population over multiple rounds, with careful monitoring of population program outcomes.	

Are results different in disease vs no-disease

Gather preliminary data to assess diagnostic accuracy

Pilot–single round. Assess impact on whole screening pathway

Implementation with post-implementation monitoring

Robert S Bresalier et al. Gut 2023;72:1904-1918

Principle 11: Accuracy required for evaluation in a screening population

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- No defined acceptable diagnostic accuracy
- Accuracy of a new non-invasive test should be at least comparable to that of non-invasive tests accepted for us in existing public health screening programmes
- Ideally improve on current FIT standard
- Phase 3 (pilot phase) will also consider factors such as uptake

Principle 12: Analytical specifications, standards and performance

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- Analytical performance characteristics of a test must be documented before assessing diagnostic value

- Eg important to know limit of detection, limit of quantification, upper limit of analytical range

- Evaluation of methods should conform to international guidance and laboratories performing screening related tests should be accredited to appropriate standards

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What is desired of a new test?

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- Be flexible, thus enabling providers to achieve desired goals of a screening programme according to demands of the healthcare environment
- Improve sensitivity for relevant neoplasia (curable CRC and advanced precursor lesions) whilst maintaining acceptable specificty
- Improve precursor lesion detection to reduce CRC incidence
- Improve participation rates

Original research

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