



WEO

The voice of world
endoscopy

Updating the new test evaluation guidelines

Carlo Senore, Robert Bresalier, Graeme P Young

Epidemiology and screening unit – CPO; University hospital Città della Salute e della Scienza, Turin, Italy

MD Anderson Cancer Center, USA

Flinders University, Australia



Centro di Riferimento per l'Epidemiologia
e la Prevenzione Oncologica in Piemonte





WEO

The voice of world
endoscopy

No conflict of interest to declare



Scope of 2016 recommendations

To develop practical advice on how best to compare “new” with proven screening tests

Recommendations for a Step-Wise Comparative Approach to the Evaluation of New Screening Tests for Colorectal Cancer

Graeme P. Young, MD, FRACP, FTSE, AGAF¹; Carlo Senore, MD, MSc²; Jack S. Mandel, PhD, MPH³;
James E. Allison, MD, FACP, AGAF⁴; Wendy S. Atkin, MPH, PhD⁵; Robert Benamouzig, MD, PhD⁶; Patrick M. M. Bossuyt, PhD⁷;
Mahinda De Silva, MB, BS, FRACP⁸; Lydia Guittet, MD, PhD⁹; Stephen P. Halloran, MBE, FRCPath¹⁰; Ulrike Haug, PhD¹¹;
Geir Hoff, MB, ChB, PhD¹²; Steven H. Itzkowitz, MD, FACP, FACG, AGAF¹³; Marcis Leja, MD, MBA, PhD, AGAF¹⁴;
Bernard Levin, MB, BCh, FACP¹⁵; Gerrit A. Meijer, MD, PhD¹⁶; Colm A. O’Morain, MD¹⁷; Susan Parry, MbChB, FRACP¹⁸;
Linda Rabeneck, MD, MPH, FRCPC¹⁹; Paul Rozen, MD^{20†}; Hiroshi Saito, MD, PhD²¹; Robert E. Schoen, MD, MPH²²;
Helen E. Seaman, BSc, PhD²³; Robert J. C. Steele, MD, FRCS²⁴; Joseph J. Y. Sung, MD, PhD²⁵; and Sidney J. Winawer, MD²⁶

Colon Cancer Screening Test Evaluation/Young et al Cancer March 15, 2016



Guiding principles

Gold standard for assessing the effectiveness of a screening method

-> RCT showing a reduction in mortality

Adoption of a new screening test requires evidence of effectiveness from a direct comparison with a proven test using intermediate outcomes, as long as the association of these outcomes to the expected health impact of screening was previously documented.

Cancer-specific mortality is not essential as an end-point, provided that the mortality benefit of the comparator has been demonstrated and that the biologic basis of detection is similar.

8 guiding principles arising from a consensus approach and a literature review



Phased evaluation

BOX 2: Study Populations and Testing Path

- **Initial testing of accuracy (Phases 1 and 2):** Ideally a single clinical group of patients undertaking *paired* testing (ie, each does both the new test and the old test), as shown in Figure 1. This is an efficient design. Initially, diagnostic verification of all cases by colonoscopy is carried out regardless of test results. Pairing reduces cohort size because of improved statistical power for assessing incremental benefit. It ensures that individuals are comparable and avoids imbalances in variables that affect test results and in other biases between the tests. If the new test demonstrates promise, then larger numbers of individuals undertaking paired testing can be further studied with colonoscopic follow-up in test-positive individuals only.
- **Subsequent testing in the screening context (Phases 3 and 4):** Individuals may be randomly assigned to do either the proven or the new test, in the context of the screening pathway, on an intention-to-screen basis, when it has been demonstrated first that the accuracy of the new test is not worse than that of a suitable, proven comparator test. When assessing test accuracy in parallel groups, the inclusion criteria for the study group must be carefully characterized and the detected lesions fully described. Without this, transferability from 1 setting to another is not possible.⁴⁰



Updating recommendations

Emerging issues to consider for revision

New developments in biomarkers/technologies

Biomarker panels and the algorithms inherent in them

Training and validation

Flexibility is required to allow tailoring the test performance parameters to local constraints / policy priorities

New biomarkers might detect prevalent lesions but also predict risk for future lesions

The target lesion

Early CRC

Advanced adenoma ? Advanced SSL? Assessing the characteristics associated with the risk of progression



Updating recommendations

Emerging issues to consider for revision

Widespread implementation of organised population based screening

How to integrate research into ongoing programs?

Characteristics of population enrolled in ongoing screening programs may influence the results

- non screening naïve population

- possible association of screening history and response to different tests

Differing approaches to the assessment of new tests adopted by regulatory authorities and by screening programs



Updating recommendations

Comparator test

FIT is the New standard: improved sensitivity for CRC and better capacity to detect (advanced) adenomas as compared to gFOBT
repeated testing improves detection

Sigmoidoscopy: comparator for the detection of pre-invasive lesions
Test offered at long intervals / once in the lifetime



Screening as a process/strategy

New test: Cut-off needs to be flexible

The demand for endoscopy resources represents one of the main determinants of the sustainability of a program.

performance should be measured

simulating different cut-off levels, focusing on the **positivity range of established population based programs**



Test evaluation framework

Preliminary assessment of the test characteristics is needed

Technical refinement of the test - New tests must meet applicable laboratory standards

Analytical validity

Test reproducibility.

Early assessment of the diagnostic accuracy of the test in the population where it is intended to be used may be justified to address spectrum bias

Stage distribution and possibly biological characteristics are different among SD cancers as compared to clinically diagnosed cancers

Predictive role of biomarkers might be different



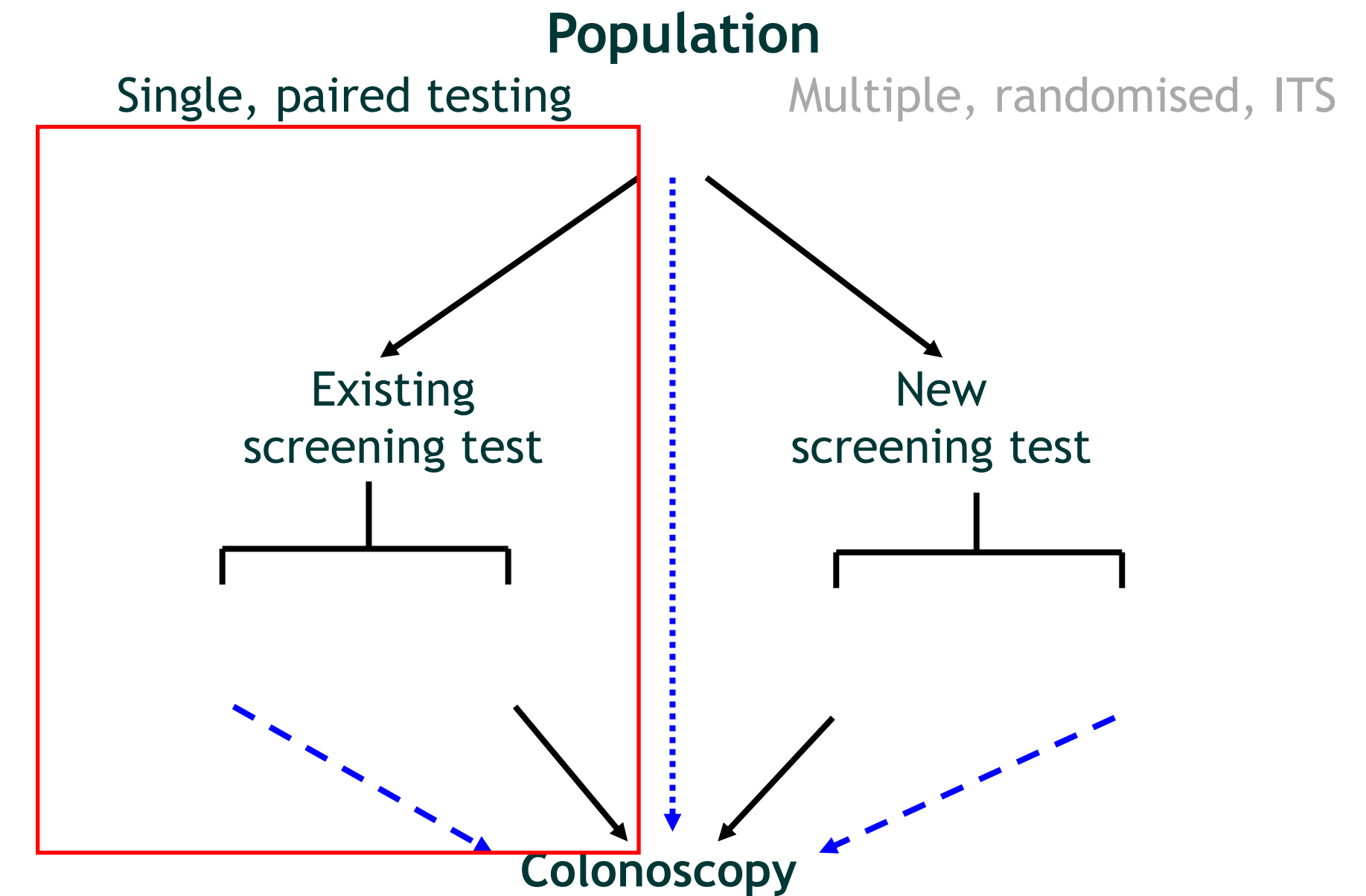
Cross-sectional evaluation

Paired testing within ongoing screening programs

All subjects are performing both the standard and the new test

immediate TC assessment of

- all subjects who are positive on the comparator test
- all (or a sub-sample of) those testing positive with the new-test only



Prospective evaluation

Performance over repeated rounds

- Outcomes of interest:
- Stage distribution of SD CRCs at first and at subsequent screening
 - Interval CRCs
 - Cumulative DR of advanced adenomas and CRC



Updating recommendations the process

Evaluation of New Tests

WEO CRC SC Expert Working Group

Tuesday, April 13, 2021 – 8.00 pm (CEST, Berlin, Amsterdam)

Corresponding Pacific Time: 11.00 am

Corresponding Eastern Time: 2.00 pm

Corresponding Sydney/Australia Time: 4.00 am/April 14, 2021

- Chairs:** Graeme Young, Carlo Senore, Robert Bresalier
- Aim:** To compile recommendations for evaluation of new screening tests having considered the new developments in technologies, widespread implementation of organized population screening and differing goals for screening and regulatory processes that apply throughout the world.
- Approach:** A revisitation of the 2016 paper with a view to producing a new document that is appropriate for 2021: This will include revision of the guiding principles, addition to these and further development of those where that is needed. There are many issues to address and this will take several meetings.

Webinar via Zoom Webinars, registered participants will receive link for meeting.

Webinar Program (CEST)

8.00 pm	Welcome by Expert Working Group Co-Chairs	<i>Graeme Young (Australia), Carlo Senore (Italy), Robert Bresalier (USA)</i>
8.05 pm	How good need the new test be?	<i>Graeme Young (Australia) Discussant: Samir Gupta (USA)</i>
8.20 pm	What is the screening target?	<i>Uri Ladabaum (USA) Discussant: Beatriz Carvalho (Netherlands)</i>
8.35 pm	Complex algorithms for test positivity criteria; approaches to address this	<i>Tim Kortlever (Netherlands) Discussant: Patrick Bossuyt (Netherlands)</i>
8.50 pm	Trial design	<i>Carlo Senore (Italy) Discussant: Lydia Guittet (France)</i>
9.05 pm	Study power and statistical approaches	<i>Ann Zuber (USA) Discussant: Patrick Bossuyt (Netherlands)</i>
9.20 pm	Feasibility of population studies and regulatory issues	<i>Robert Bresalier (USA) Discussant: Robert Steele (UK)</i>
9.35 pm	Meeting adjourns	



Updating recommendations the process

Consensus process following a modified Delphi approach

A table including the set of guiding principles to be revised has been sent to panellists agreeing to contribute in this project

This consensus round, conducted by email, targets an expanded group that also includes those who expressed interest in the April Webinar and those who presented at it.

A revised paper will be prepared reporting the results of the process



Updating recommendations consulting the industry

We are asking industry to provide us with their views as to how regulatory bodies approve tests.

Industry will not be involved in the definition of the content of the revised recommendations.

Some feedback seems useful to know which are the problems companies are facing when interacting with regulatory agencies.



Joint webinar

FIT for screening and Evaluation of new tests EWGs

November 16th



Thank you for your attention

carlo.senore@cpo.it





WEO

World Endoscopy
Organization

