WEO

The voice of world endoscopy

Design of trials going forward

Carlo Senore

Epidemiology and screening unit – CPO

University hospital Città della Salute e della Scienza, Turin, Italy

CPO

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

WEO

The voice of world endoscopy

No conflict of interest to declare

Setting

Average risk subjects targeted for screening

population based setting

.

Performance as a result of

Test characteristics + positivity threshold + interval

Blood Based Screening

Colorectal Cancer

Multi Cancer

Test evaluation framework

Preliminary assessment of the test characteristics is needed

New tests must meet established laboratory standards

Analytical validity

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

Cases and controls should ideally be recruited in a screening population

Test evaluation framework

Diagnostic Accuracy

Measured against a reference standard

Cross sectional design

Clinical utility

Effectiveness and harms over the spectrum of disease

Prospective design

The study sample should be representative of the population where the test is intended to be used

Comparator test

FIT New standard: improved sensitivity for CRC and better capacity to detect (advanced) adenomas
repeated testing *improves detection*

Sigmoidoscopy: comparator for tests aimed to detect 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

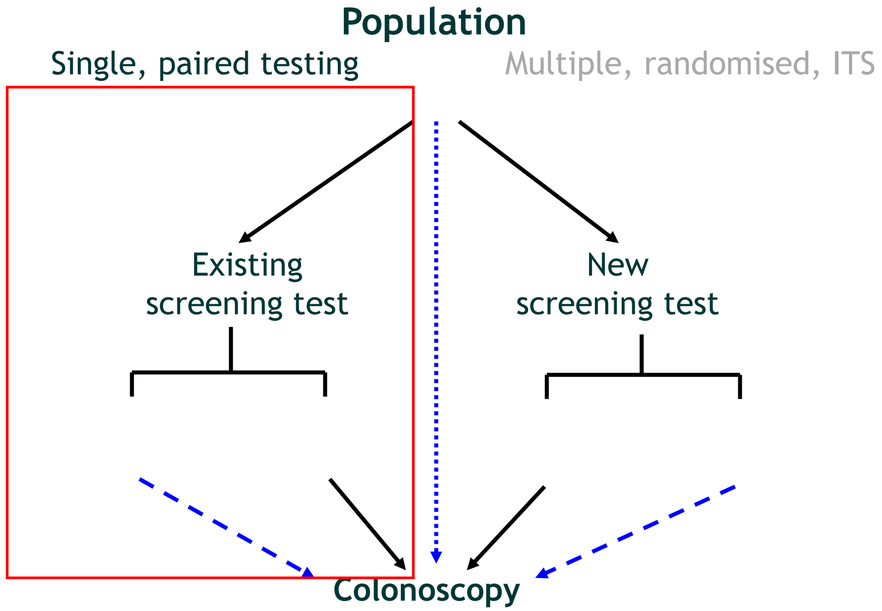
Paired testing within ongoing screening programs

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



3. Initial screening evaluations, single screen	Characteristics of disease detected are defined and false-referral rate identified. Acceptability, workloads.	Testing in a typical screening environment in separate cohorts. Include intention-to-screen analyses. N=600 (assessing participation rates) or N=10,000 (assessing relative performance)

Prospective evaluation

Outcome of interest: CRC detection *Stage distribution of SD CRCs at first and at subsequent screening*

Detection of early stage lesions is a goal, but screening may increase the detection of indolent lesions

A more favourable stage distribution, or a reduction in the absolute risk of late stage diagnosis, may be expected among subjects with previous negative exams, if the test can detect lesions at higher risk of progression

Interval CRCs

Table 1. Comparison of Four Fecal Occult-Blood Tests in 8104 People.

Test and Finding	Neoplasms Detected	True Positive Test	False Positive Test	True Negative Test	False Negative Test
	no.		*no. of patients (%)**		
Hemoccult II (8065 screened, 198 [2.5%] positive)					
Carcinoma	35	13 (0.2)	185 (2.3)	7845 (97.3)	22 (0.3)
Polyp ≥1 cm	107	33 (0.4)	152 (1.9)	7771 (96.8)	74 (0.9)
Combined	142	46 (0.6)	152 (1.9)	7771 (96.4)	96 (1.2)
Hemoccult II Sensa (7904 screened, 1073 [13.6%] positive)					
Carcinoma	34	27 (0.3)	1046 (13.2)	6824 (86.3)	7 (0.1)
Polyp ≥1 cm	105	72 (0.9)	974 (12.4)	6791 (86.3)	33 (0.4)
Combined	139	99 (1.3)	974 (12.3)	6791 (85.9)	40 (0.5)
HemeSelect (7493 screened, 440 [5.9%] positive)					
Carcinoma	32	22 (0.3)	418 (5.6)	7043 (94.0)	10 (0.1)
Polyp ≥1 cm	102	68 (0.9)	350 (4.7)	7009 (93.9)	34 (0.5)
Combined	134	90 (1.2)	350 (4.7)	7009 (93.5)	44 (0.6)
Combination (Hemoccult II Sensa and HemeSelect) (7847 screened, 233 [3.0%] positive)					
Carcinoma	32	21 (0.3)	212 (2.7)	7603 (96.9)	11 (0.1)
Polyp ≥1 cm	102	51 (0.7)	161 (2.1)	7552 (96.6)	51 (0.7)
Combined	134	72 (0.9)	161 (2.1)	7552 (96.2)	62 (0.8)

*For carcinoma the percentages are based on the number of patients screened. For polyps the percentages are based on the number of patients screened minus the number with carcinoma detected on colonoscopy.

Allison J et al. NEJM 1996

Multi cancer tests

Two main scenarios

The test detects cancers for which a validated screening test is available

Standard Of Care (SOC) screening

The test detects cancers for which no proven screening test is available

Comparative evaluation pan cancer test – SOC screening

Cross-sectional design to compare diagnostic accuracy - Paired testing

Phased evaluation approach as described for the evaluation of new CRC screening tests

Comparative evaluation pan cancer test – SOC screening

Additional aims

Assessing the potential increase in population coverage when offering blood test to non responders to SOC screening

Pan cancer test as a triage test ?

Example: orient management of screen detected lung nodules at spiral CT screening

Pan cancer test – no validated screening test available

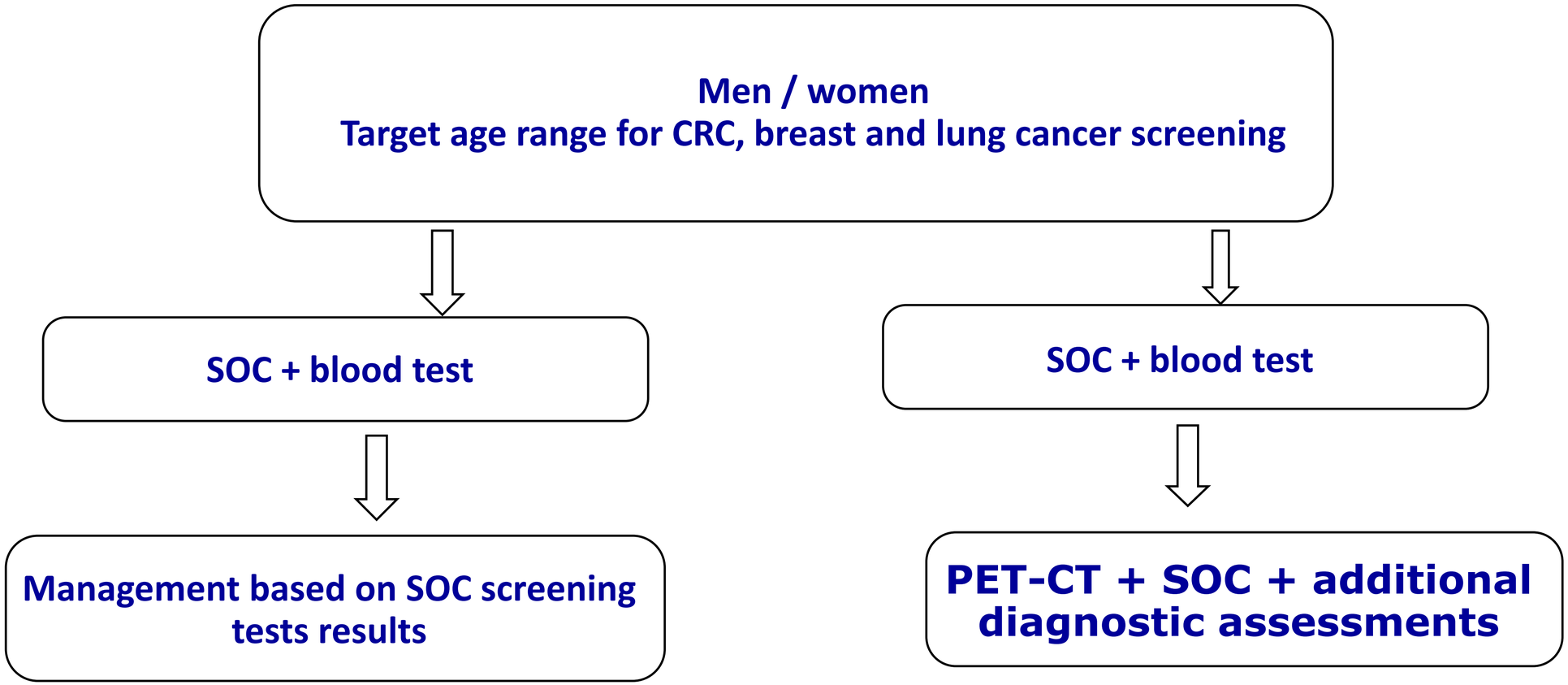
Pan cancer test detects cancers for which no validated screening test is available

…… **we cannot be certain** that that the **DETECT-A blood test** used in our study **helped any patient**

(Lennon AM et al Science 2020)

Phased approach not applicable

RCT having mortality as end-point



intermediate outcomes : stage distribution of cancers detected in the blood test group and in the usual care group

Pan cancer test – no validated screening test available

Open issues

Target population

Average risk versus high-risk subjects

Screening interval

Screening interval for blood tests needs to be defined

Integrating SOC screening

Test evaluation

Organized screening programs represent an ideal platform to implement comparative effectiveness research

The framework of learning screening programs, adopting a randomized design to assess the effectiveness of changes within ongoing established programs might facilitate the comparative assessment of new technologies.

(Arbyn M et al. Eds. 2007; Hakama M et al. 2012; Holme O et al. 2020)

Longitudinal samples repositories, integrated with risk factor data, may accelerate the development of new cancer screening technologies

Thank you to

Graeme Young
Ulrike Haug
Lydia Guittet
Nereo Segnan
Robert Schoen

Thank you for your attention

carlo.senore@cpo.it

WEO

World Endoscopy Organization