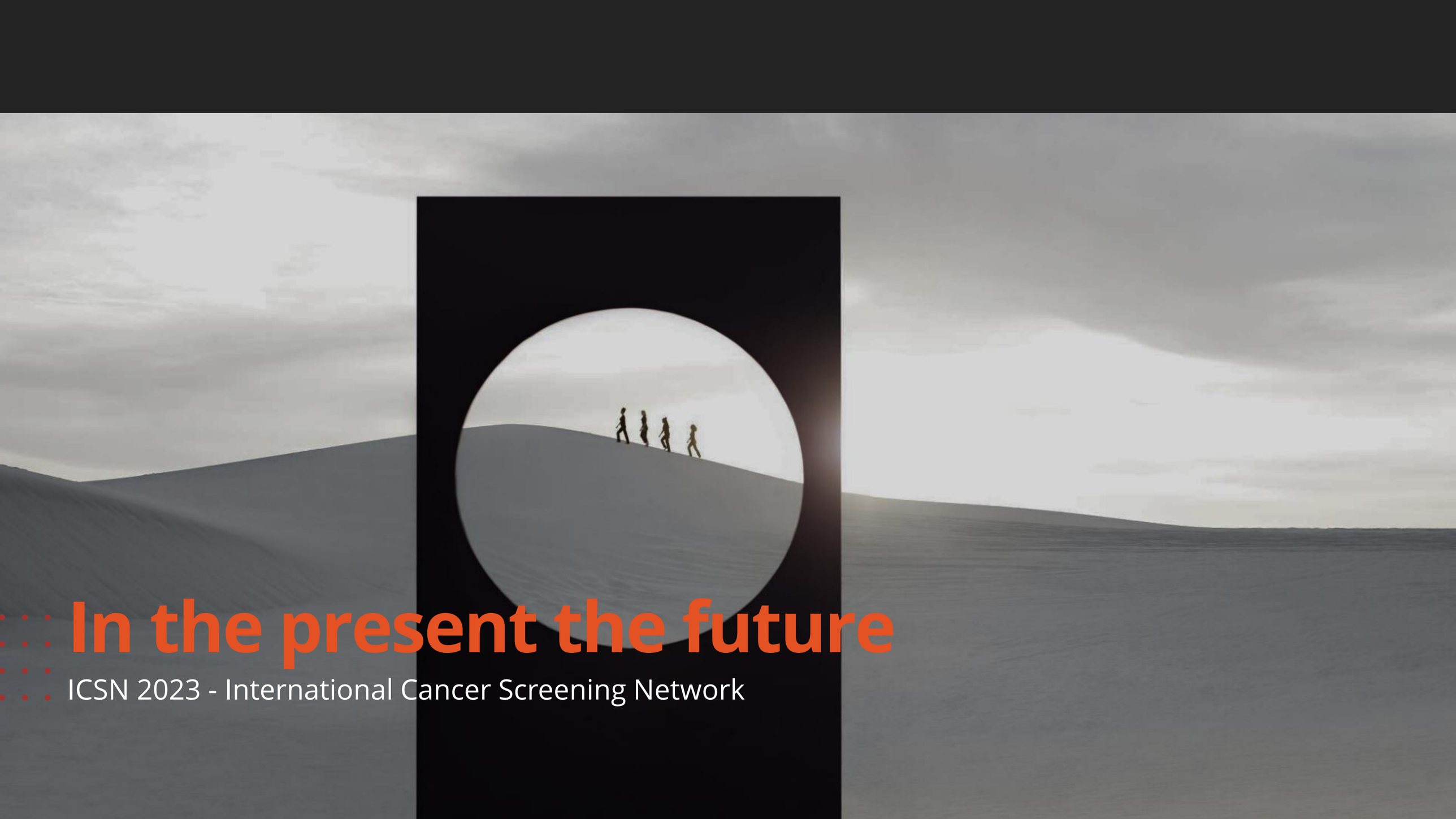

In the present the future

ICSN 2023 - International Cancer Screening Network

ICSN2023
Cancer screening: in the present, the future
June 21-23, 2023 | Turin (Italy)

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

AZIENDA OSPEDALIERO - UNIVERSITARIA
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Something to refine in cancer screening

Key note speech

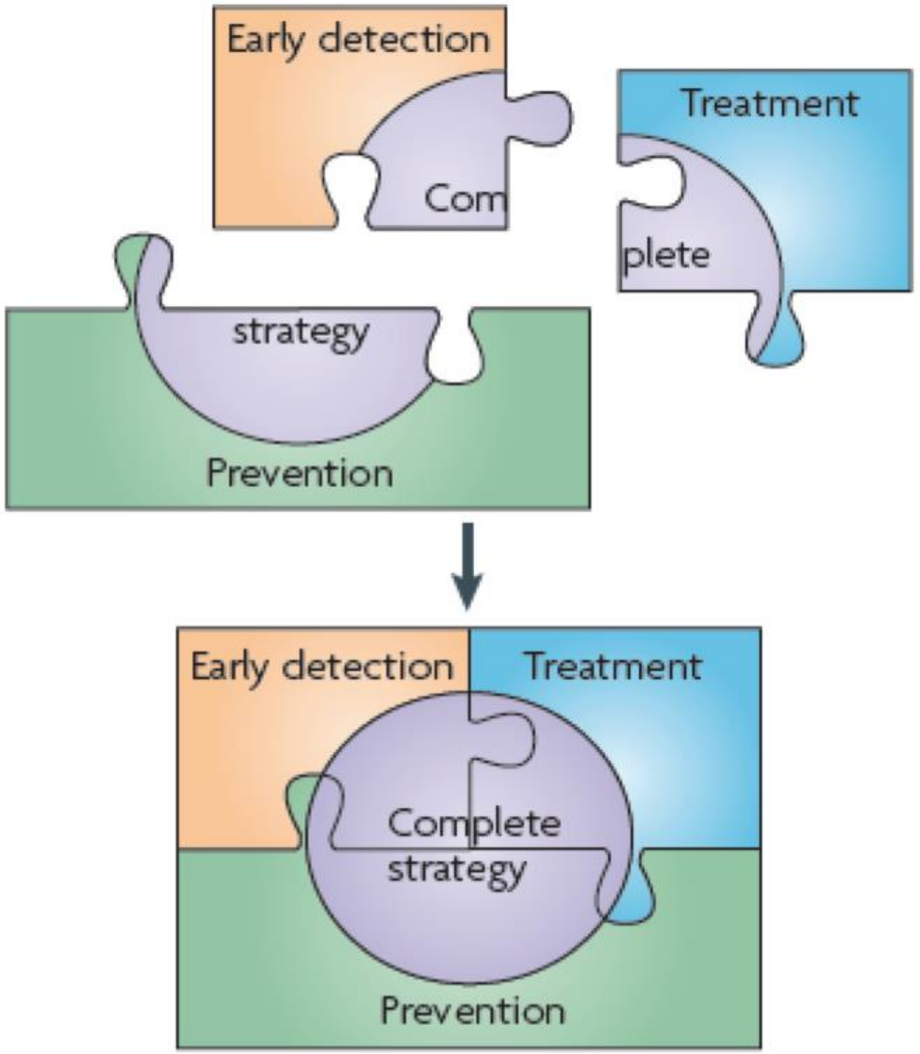
Nereo Segnan M.D. Msc - CPO Piemonte

No conflicts of interest to declare

1.Understand the framework

Cancer screening is a a tool of the strategy for cancer elimination, where prevention, early detection and treatment are the interconnected, not indipendent components.

Prevention, early detection and treatment interconnections are the fundamental framework


Early detection
Com
Treatment
plete
strategy
Prevention
Early detection
Treatment
Complete
strategy
Prevention

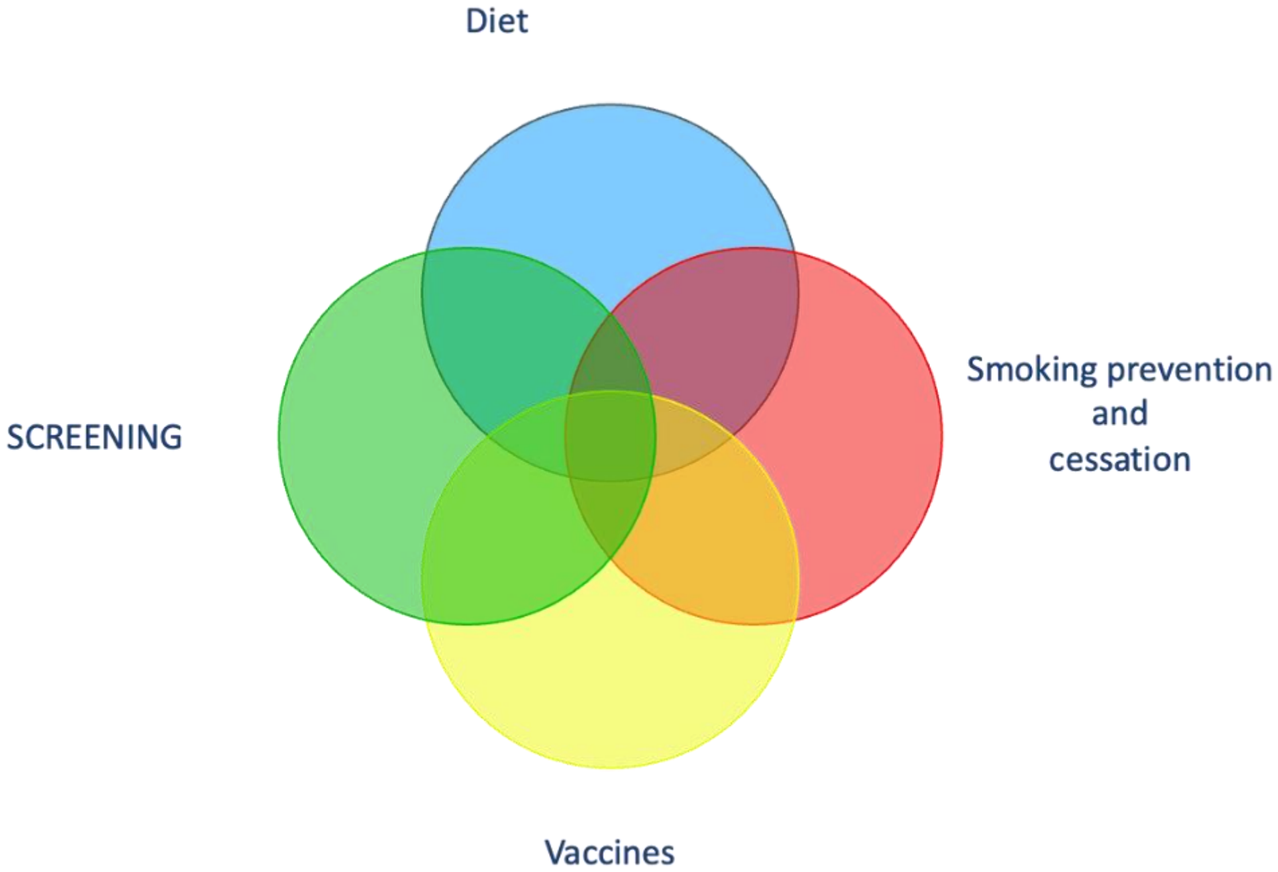
Cancer screening:

- prevents cancer (ex colorectal, cervix uteri, ….) reducing incidence and morbidity
- reduces mortality by stage shifting (colorectal, breast ……)

Primary prevention interventions (smoking prevention and cessation, physical exercize, healthy diet…), vaccines reduce cancer incidence and morbidity.

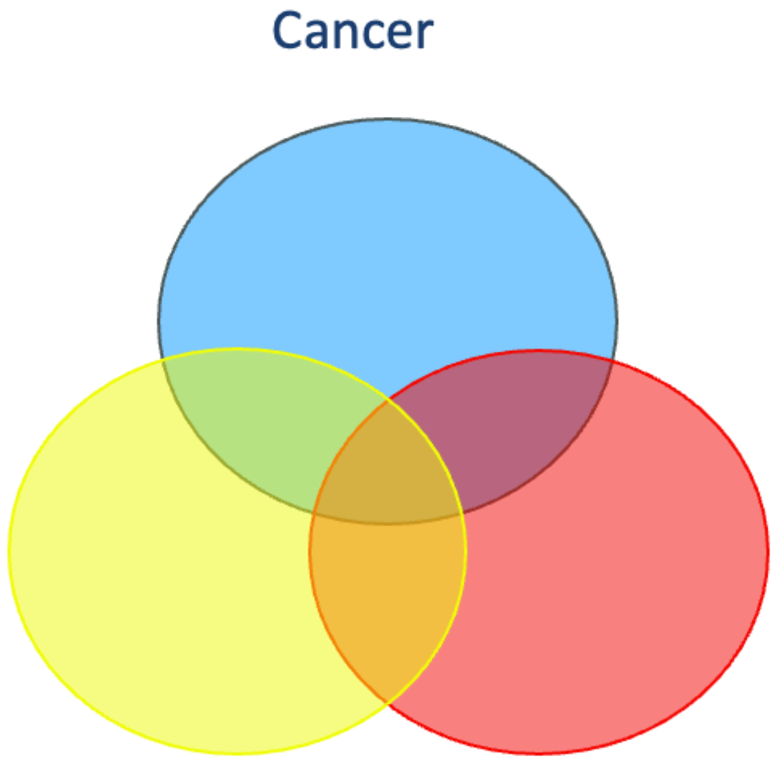
Screening and primary prevention target the same individuals and the same conditions. When applied, they are synergic.

Primary and secondary prevention interventions target the same individual.



Only cancer?

The same risk factor may cause many chronic diseases which affect the same individual



Comorbidities

CANCER RESEARCH | POPULATION AND PREVENTION SCIENCE

A Systematic Review and Multilevel Regression Analysis Reveals the Comorbidity Prevalence in Cancer

Cilla E.J. Vrinzen[1,2], Linn Delfgou[1], Niek Stadhouders[1], Rosella P.M.G. Hermens[1], Matthias A.W. Merkx[1,2], Haiko J. Bloemendal[3], and Patrick P.T. Jeurissen[1]

«The weighted average comorbidity prevalence was 33.4%, and comorbidities were the most common in lung cancer (46.7%) and colorectal cancer (40.0%), followed by prostate cancer (28.5%), melanoma cancer (28.3%), and breast cancer (22.4%). The most common types of comorbidities were hypertension (29.7%), pulmonary diseases (15.9%), and diabetes (13.5%)"

Cancer Res 2023;83:1147–57

The comorbidities change the screening outcomes and benefits

How to adapt the cancer screening programmes to this framework?

- ***Equity: reduce and eliminate economic, cultural, social barriers***

  Is it ethically acceptable to pay for something that we are asked to do? Vaccines are free of charge, cancer screening?

- ***Change the organization:***

Integration of cancer screening in primary prevention and health care.

- ***Change the paradigma:***

Cancer Screening is a process as part of wider process together with prevention and health care.

2. Screening: what news?

-Risk based screening, AI in .....
-MCED Multi Cancer Early Detection

npj | Precision Oncology

www.nature.com/npjprecisiononcology

PERSPECTIVE OPEN

Universal cancer screening: revolutionary, rational, and realizable

David A. Ahlquist[1]

npj Precision Oncology (2018)2:23

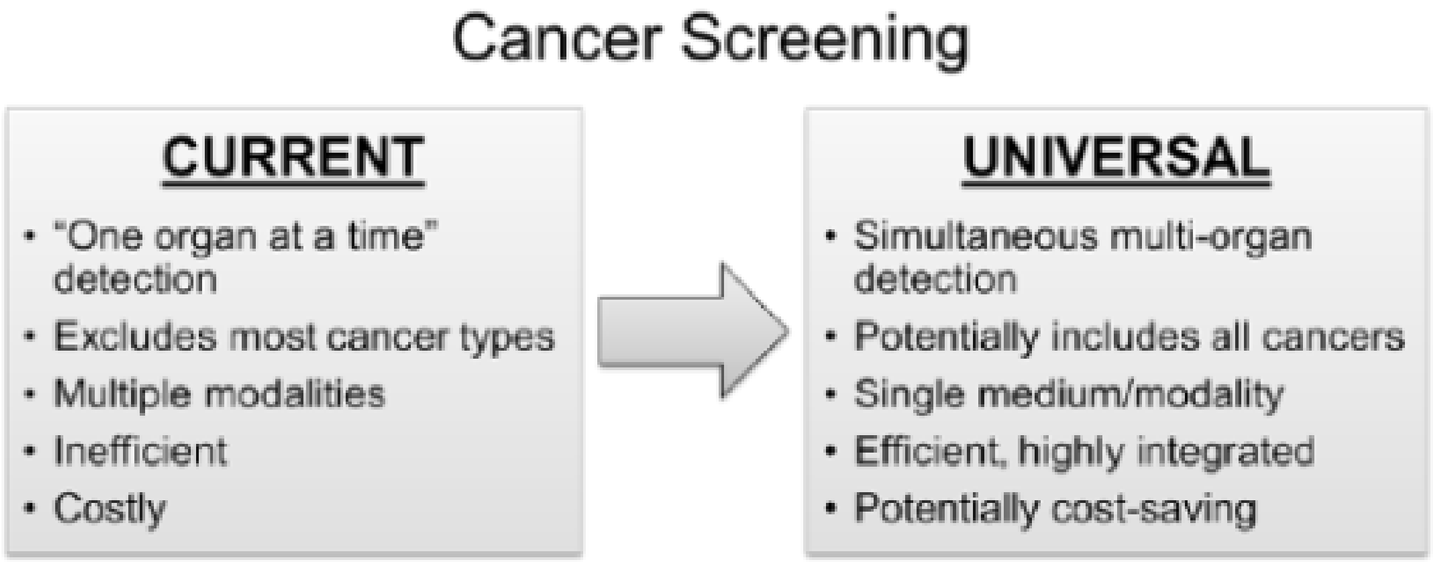


Fig. 1 Current single-organ and future universal cancer screening approaches: a conceptual comparison of features

Klein EA, Richards D, Cohn A, et al. Clinical validation of a targeted methylation-based multi-cancer early detection test using an independent validation set. *Ann Oncol*. 2021;32(9):1167-1177.

Specificity for *cancer signal detection was 99.5%* *[95% confidence interval (CI): 99.0% to 99.8%].*

Overall sensitivity for cancer signal detection was 51.5% *(49.6% to 53.3%);* *sensitivity increased with stage [stage I: 16.8% (14.5% to* 19.5%), stage II: 40.4% (36.8% to 44.1%), stage III: 77.0% (73.4% to 80.3%), stage IV: 90.1% (87.5% to 92.2%)].

Stage I-III sensitivity was 67.6% (64.4% to 70.6%) in 12 pre-specified cancers that account for approximately two-thirds of annual USA cancer deaths and was 40.7% (38.7% to 42.9%) in all cancers. Cancer signals were detected across >50 cancer types. Overall accuracy of CSO prediction in true positives was 88.7% (87.0% to 90.2%).

British Journal of Cancer

www.nature.com/bjc

ARTICLE OPEN

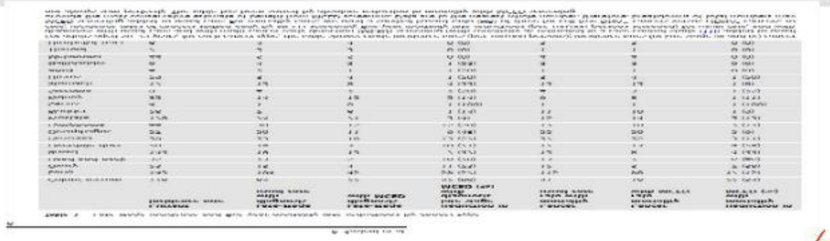
Check for updates

Modelled mortality benefits of multi-cancer early detection screening in England

Peter Sasieni[1], Rebecca Smittenaar[2], Earl Hubbell[3], John Broggio[4], Richard D. Neal[5] and Charles Swanton[6,7]

RESULTS: Estimated late-stage and mortality reductions were robust to a range of assumptions. With the least favourable dwell (sojourn) time and cfDNA status hazard ratio assumptions, we estimated, among 100,000 screened individuals, 67 (17%) fewer cancer deaths per year corresponding to 2029 fewer deaths in those screened between ages 50–79 years.

CONCLUSION: Realising the potential benefits of MCED tests could substantially reduce late-stage cancer diagnoses and mortality.



OXFORD

JNCI: Journal Of The National Cancer Institute, 2023, 115(3), 250–257
https://doi.org/10.1093/jnci/djac218
Advance Access Publication Date: 2 December 2022
Commentary

Study design considerations for trials to evaluate multicancer early detection assays for clinical utility

Lori M. Minasian, MD,[1*] Paul Pinsky, PhD,[1] Hormuzd A. Katki, PhD,[2] Tony Dickherber, PhD,[3] Paul K. J. Han, MD,[4] Lyndsay Harris, MD,[5] Christos Patriotis, PhD,[1] Sudhir Srivastava, PhD,[1] Carol J. Weil, JD,[1] Philip C. Prorok, PhD,[1] Philip E. Castle, PhD, MPH[1]

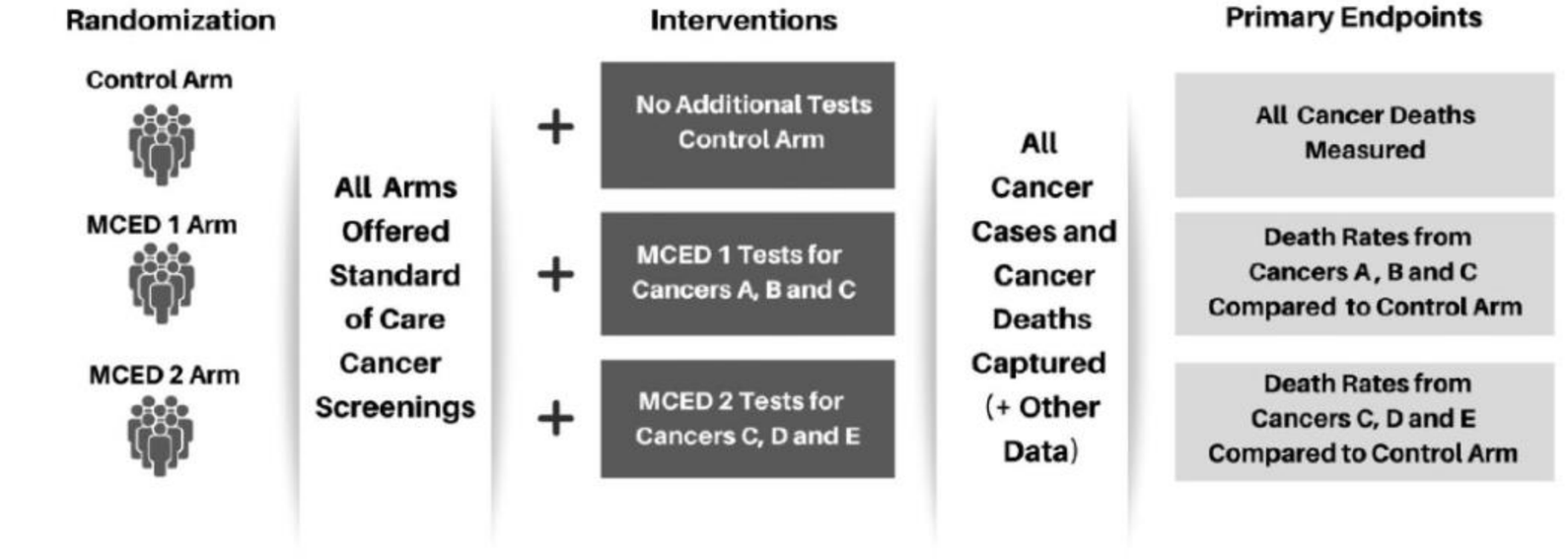
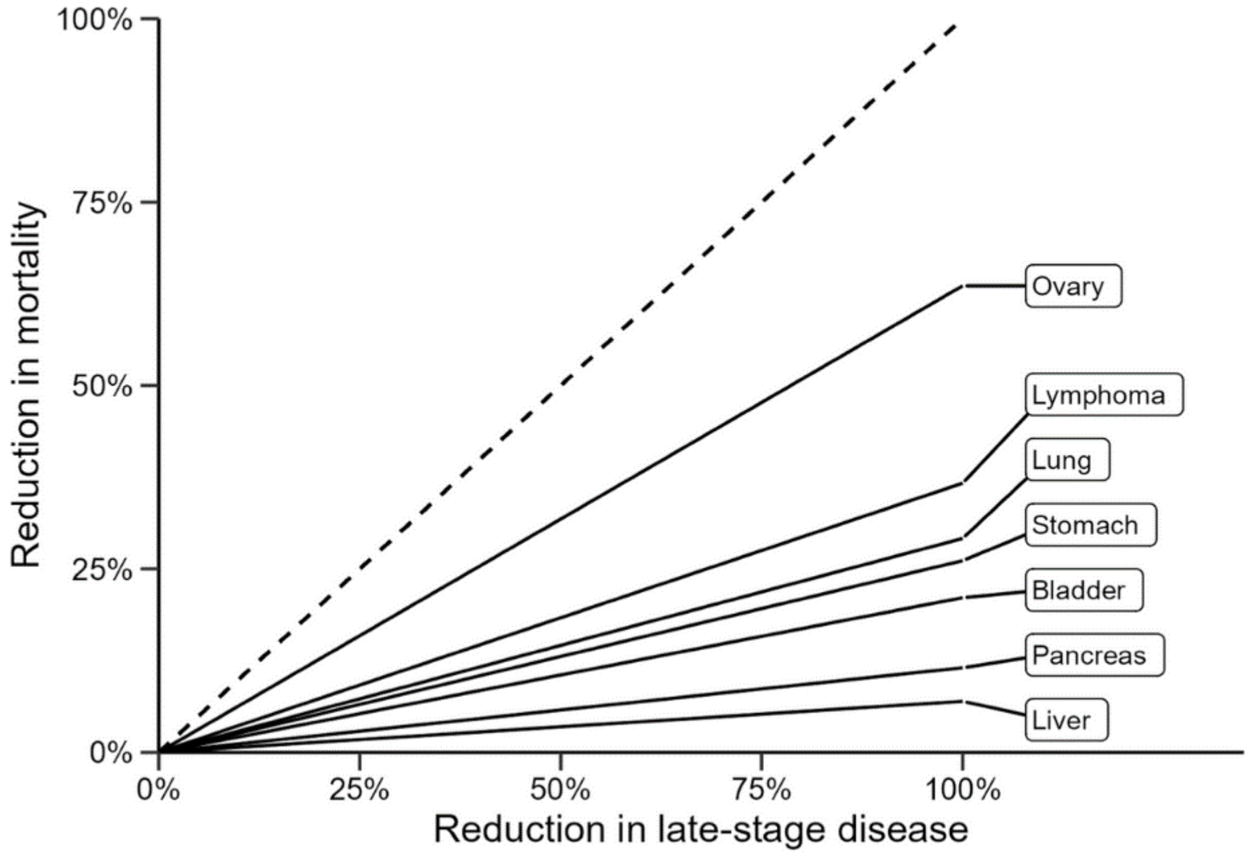


Figure 1. Platform study design schema. MCED = multicancer early detection



Cancer Epidemiol Biomarkers Prev. 2022 July 01; 31(7): 1298–1304.?Stage Shift as an Endpoint in Cancer Screening Trials: Implications for Evaluating Multi-Cancer Early Detection Tests?
Lukas Owens, Roman Gulati, Ruth Etzion

"The figure shows that the same reduction in late-stage disease has a different implication for mortality depending on the characteristics of the cancer. For example, in ovarian cancer, ρ = 0.636, so a 20% reduction in late-stage disease is expected to result in a 13% mortality reduction, but for liver cancer, the value of the stage-shift multiplier is only 0.070, so a similar 20% reduction in late-stage disease would be expected to produce a 1% mortality reduction

- In MCED, any mortality benefit is likely to vary substantially across target cancers. Stage shift does not appear to be a reliable basis for inference about mortality reduction across cancers potentially detectable by MCED tests.

- Impact: Stage shift may be an appealing endpoint for evaluation of cancer screening tests but it appears to be an unreliable predictor of mortality benefit; further, the same stage shift can mean different things for different cancers.”

- MCED and Detection of precursors lesions?

- Eighty % of the reduction of mortality (avoided death) for colorectal cancer is due to precursors lesions removal (adenomas) and 20% to stage shifting.

At the moment MCED may reduce cancer mortality not cancer incidence.

- Low sensitivity for early stages

- MCED and primary prevention: blood sample easier to take than to introduce behavioural changes or environmental prevention.

3. Metrics A

What to measure?
Effectiveness as Harms to Benefits balance

- **Process indicators (coverage by invitation, testing, positivity, detection rates, predictive values, process time intervals), intermediate outcomes (stage distributions, ……) are necessary for monitoring and quality improving of cancer screening.**

They have to be comparable in different areas and time periods (see point 3B – Consortium)

- **Incidence and/or mortality reduction is a necessary but not sufficient condition for adopting cancer screening. The harms to benefits balance should be favourable to screening**

The balance of harms and benefits is difficult to assess and to compare across different cancer screenings .

At individual level values and expectations are different, at population level cancer screening may differ over different populations. The screening programs may adopt different tests, cut off, intervals and diagnostic assessment.

The determinants of the harms/benefits balance may vary as size and compositions

Until now the harms/benefits balance measures involved only the Harms/Benefits balance in organized screening settings and not opportunistic screening or unscreened persons

How to quantify and to measure the harms/benefits balance?

DALY's is a composite indicator, taking into account death and disability (specular to survival and quality of life)

DALY's estimates can be used as a common and unique measure to compare harms of screening (and prevention), clinical assessment and treatment (and by default absence of harms i.e. benefits) in population groups:

- **organized screening (group 1)**
- **opportunistic screening (group 2)**
- **unscreened persons (group 3)**

Disability Adjusted Life Years (DALYs)

$$DALY = YLL + YLD$$

where:

YLL = years of life lost due to premature mortality

YLD = years lived with disability.

The estimated number of DALYs for screened and unscreened persons can be compared for the cancer screening(s) of interest.

The DALY's depending or associated with screening harms are included in the point estimates, comprising also DALY's eventually due to **lead time** and **over-diagnosis.**

The global burden of cancer attributable to risk factors, 2010–19: a systematic analysis for the Global Burden of Disease Study 2019

GBD 2019 Cancer Risk Factors Collaborators*

Summary

Background Understanding the magnitude of cancer burden attributable to potentially modifiable risk factors is crucial for development of effective prevention and mitigation strategies. We analysed results from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019 to inform cancer control planning efforts globally.

Lancet 2022; 400: 563–91

See Comment page 540

*Collaborators are listed at th

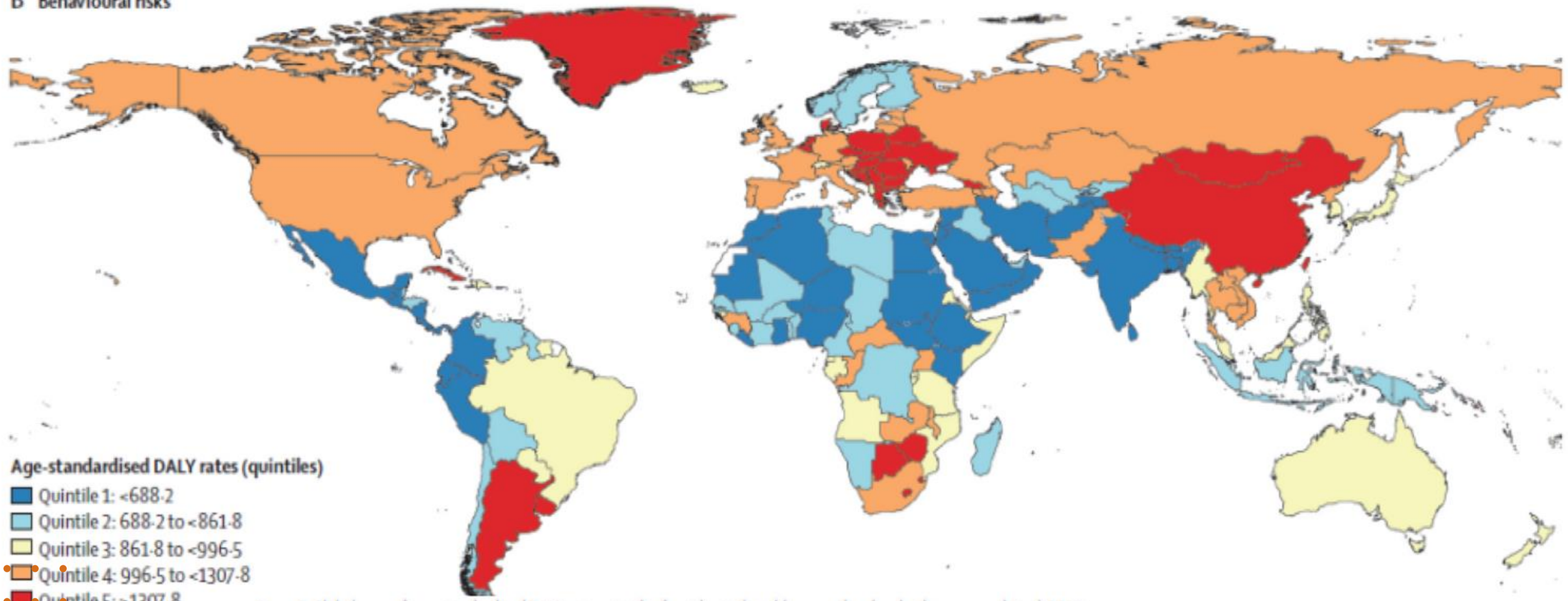


Figure 3: Global map of age-standardised DALY rate quintiles for risk-attributable cancer burden, both sexes combined, 2019

(A) Environmental and occupational risks. (B) Behavioural risks. (C) Metabolic risks. Each map represents estimates at the national level. Quintiles are based on age-standardised DALY rates per 100 000 person-years. See appendix (pp 165–68, 234–39) for further details of risk-attributable cancer deaths and DALYs for each country and territory. DALYs=disability-adjusted life-years.

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3. Metrics B

Screening comparisons: ICSN Consortium

Gastroenterology
Volume 162, Issue 3, March 2022, Pages 668-674

Commentary

Comparing Colorectal Cancer Screening Outcomes in the International Cancer Screening Network: A Consortium Proposal

Nereo Segnan, Evelien Dekker, V.Paul Doria-Rose, Carlo Senore, Linda Rabeneck, Iris Lansdorp-Vogelaar, International Cancer Screening Network Colorectal Cancer Screening Working Group

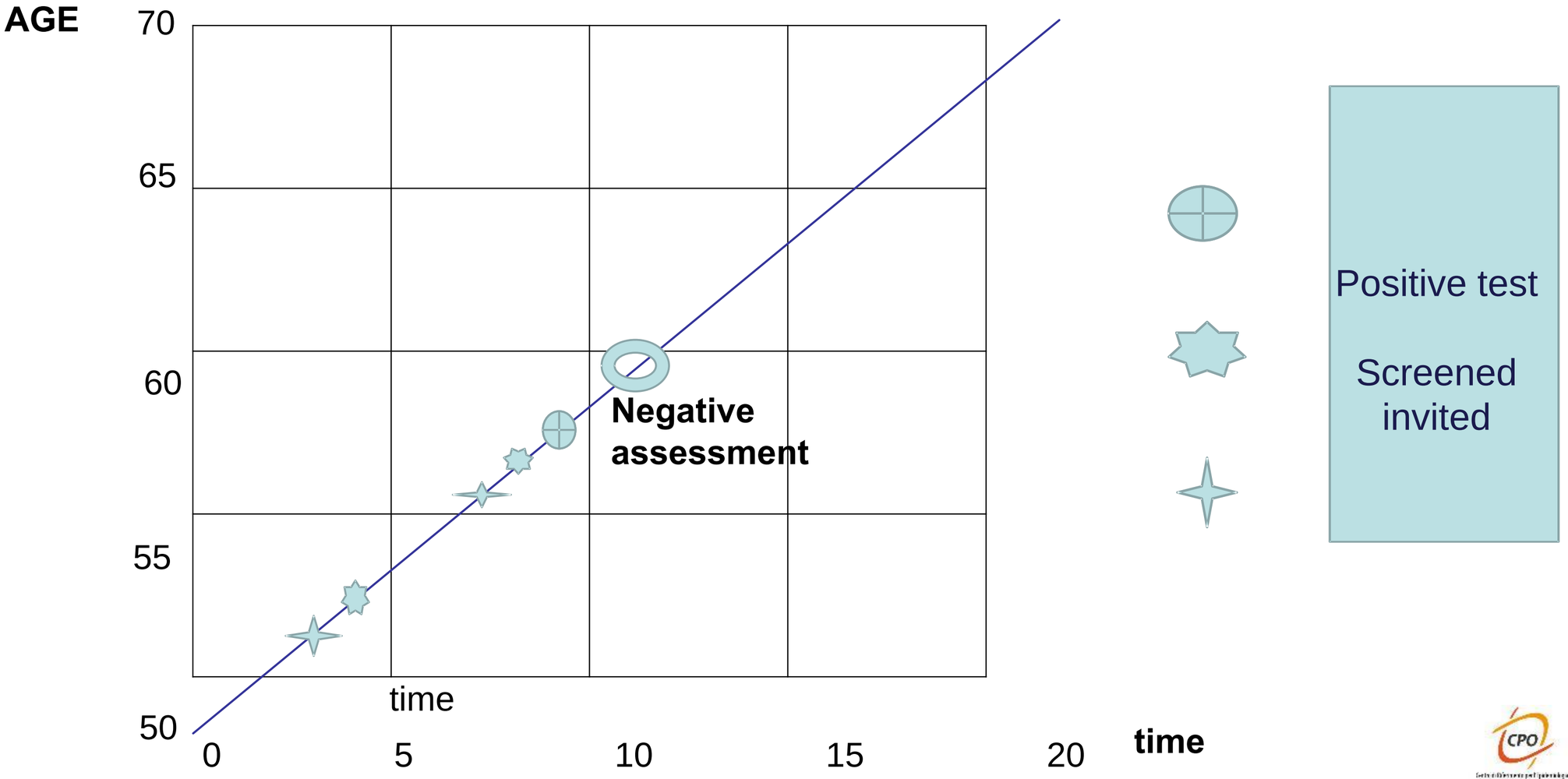
Screening Comparability requirements

A. Commensurable intervals. The outcomes (coverage by invitation, coverage by testing , positivity rate, detection rates , stages distribution, incidence , mortality) are not comparable without taking into account commensurable (comparable) intervals and the actual screening histories of the eligible population.

B. Actual screening histories: Individual screening histories are not strictly respecting the established screening schedules. Different screening tests may co-exist

- **To record the actual dates of the events associated with screening, would measure the correct intervals between the events, classifying the events (type of test, blood concentration, type of lesions , diagnosis…… and the relevant related information.**

Individual's screening history contribution when using a dynamic (active intake) screening cohort approach to compare different screening programs



Outcomes measured as incidence density or cumulative incidence by calendar period and age group:
- coverage rates by invitation, testing
- positivity rates, detection rates, stage distribution
- CRC incidence, mortality
- .....

It seems appropriate to adopt standard time intervals (for example ten years) to compare the medium term outcomes (example: cumulative detection rates of cancer and advanced adenomas), achieved by different type and/or interval screening tests during the same period

This international consortium would be open to all types of screening programs, including opportunistic, as long as they are able to provide the necessary data on screening, and the rules around data provision, sharing and analysis are to be defined in the bylaws of the consortium beforehand, taking into account the different regulatory systems.
We realize that the Global Data Protection Regulation and similar privacy regulations may hamper the ability to share individual-level data.

This model would be agnostic to data sources and flexible enough to accommodate researchers and institutions.

The added value of this approach would be the participation in the definition of the research objectives, in the analysis of databases, of all consortium screening members while training consortium participants on how to better refine their data and programmes.

A federated data system like the Virtual Data Warehouse of the Health Care System Research Network or the Observational Medical Outcomes Partnership of Observational Health Data Sciences and Informatics - **https://ohdsi.github.io/TheBookOfOhdsi/CommonDataModel.html** - could be used.

In this approach, individual-level data remain at their original source but are transformed into a common format to facilitate distributed analysis and aggregation of results.

The experience of the PROSPR consortium, aimed to promote multisite research on CRC screening while sharing data collected and organized at multiple levels, already has shown that pooling and sharing data to conduct collaborative research and evaluation is feasible.

EU Cost Action

We propose to structure **an International multidisciplinary Consortium of CRC screening programs** aiming to implement a common accessible database, in order to generate comparable estimates of indicators and outcomes of CRC across different programs and countries.
Such consortium will promote the collaboration..... for:

1. Harmonising and bringing together the data from the different programs in one database,

2. Defining a computational approach to extract the relevant indicators accounting for differences between programs

3. Addressing ethical and legal aspects related to data sharing for the purposes of comparative evaluation, benchmarking and research, in the context of international initiatives.

4. Maintaining a sustainable collaborative network that ensures optimal exchange of knowledge to keep CRC screening up-to-date

The Consortium approach can be adopted for all cancer screenings.

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Città della Salute e della Scienza di Torino

Thank you
for the attention

Nereo Segnan M.D. Msc - CPO Piemonte

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