

Risk-Stratified Screening: Applications to New Screening Programmes

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Disclosure

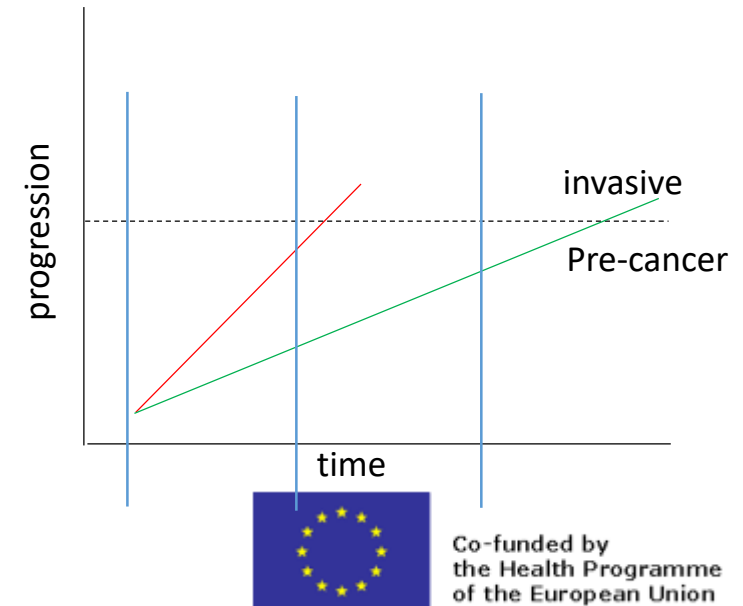
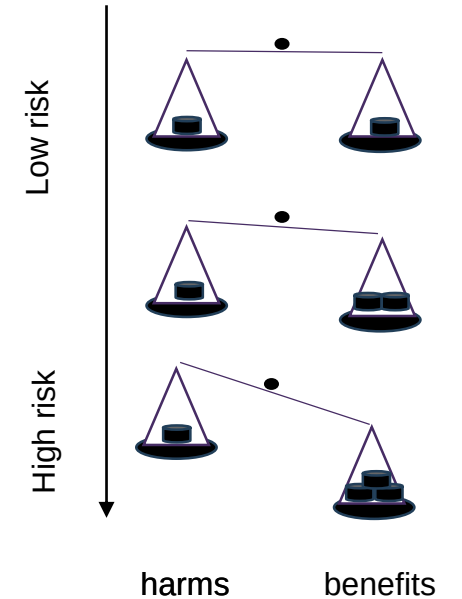
- Non-financial support for independent study from:
 - iCAD: software for an independent study, promoted by the Karolinska Institutet
 - GE: loan of two mammography machines to support recruitment in the REtomo study, funded by the Emilia-Romagna Regional Health Authority and the Italian Ministry of Health
 - As PI of an Independent study, funded by the Italian Ministry of Health, I conducted negotiations to obtain reagents at a reduced price or for free with Hologic, Roche, Becton Dickinson
 - I am consulting IARC for the EC-CvC and I am a member of the guidelines developing group
 - I am consulting JRC for the ECICC and I am a member of the guidelines developing group

Topics of the presentation

- Why a risk stratified screening?
- The conceptual framework
- Putting the risk stratification opportunities in the framework
 - Lung cancer screening
 - Prostate cancer screening
 - Gastric cancer

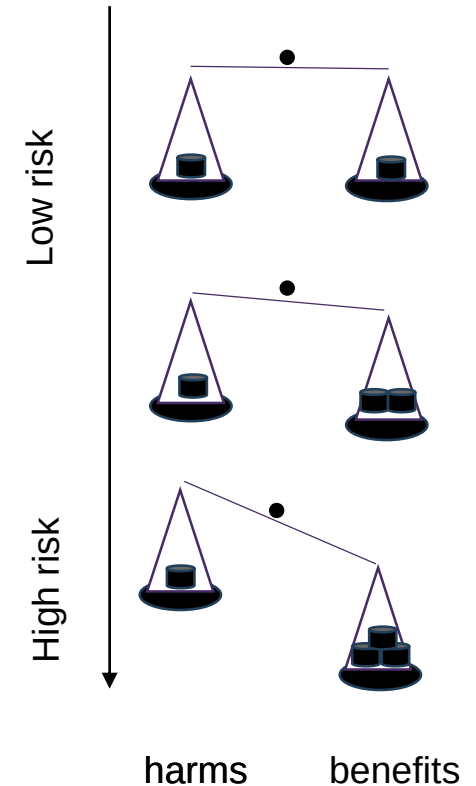
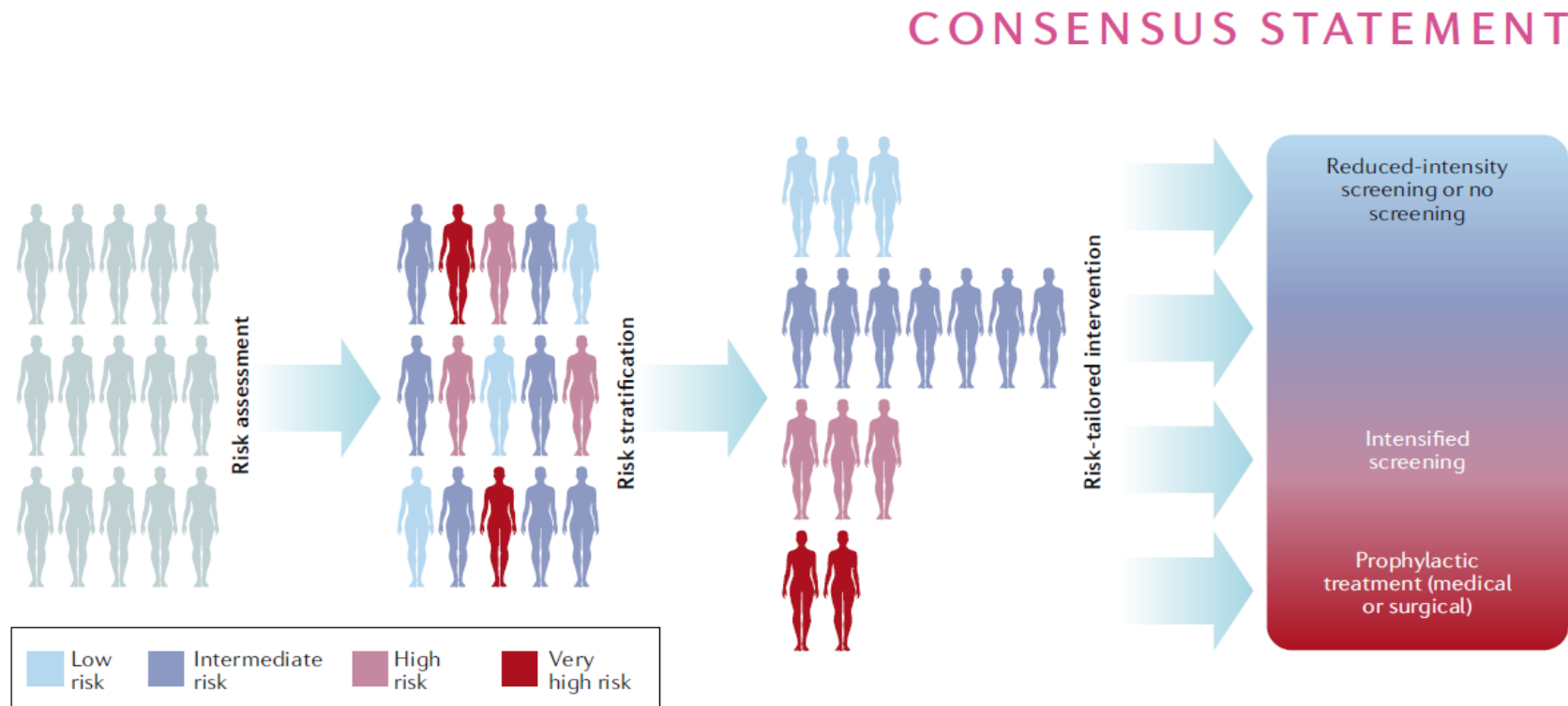
The rationale

- Benefits are for those who develop the disease, thus proportional to the proportional risk
- Harms affect all the screenees, thus harms/benefits ratio depends on risk
 - **Risk stratification can optimize the balance**
- A different risk may also imply a different natural history of the disease
 - **In this case, a different screening (interval, age to start or test) may increase the screening efficacy**



The Conceptual framework: what we need

- Valid information to assess the individual (or population) risk
- Possiamo definire gruppi omogenei di rischio
- A cui attribuire un protocollo di screening differente



Screening is a pathway



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P. Giorgi Rossi et al.

European Journal of Cancer 240 (2026) 116746

OBJECTIVES

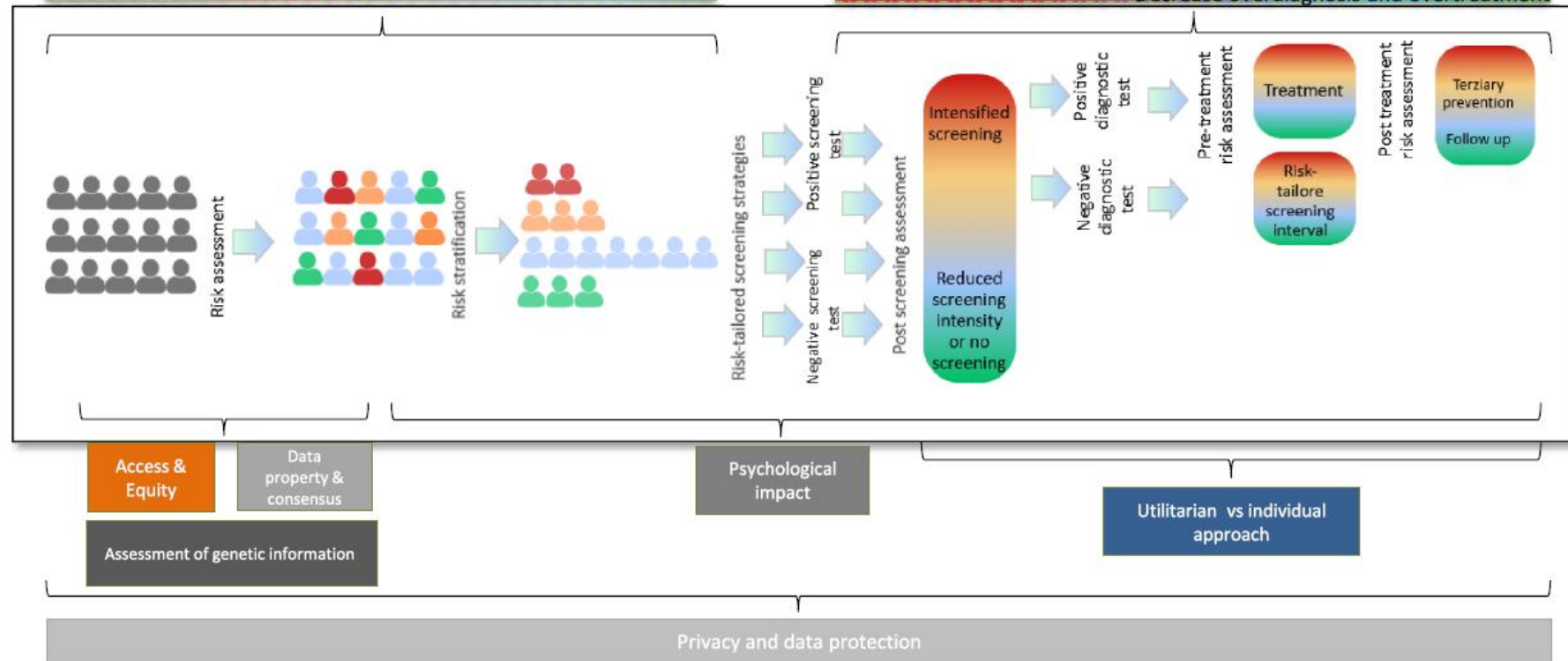
- Reduce cancer-specific mortality and, where possible, overall incidence
- Reduce the incidence of advanced cancers, increase the detection of precancerous lesions, and decrease interval cancers and late-stage diagnoses
- Ensure or enhance sustainability through feasible and scalable solutions

- Improve equity while avoiding discrimination

- Ensure correct information, promote shared decision

- Increased benefits

- Decrease false-positive and unnecessary invasive procedures
- Decrease overdiagnosis and overtreatment



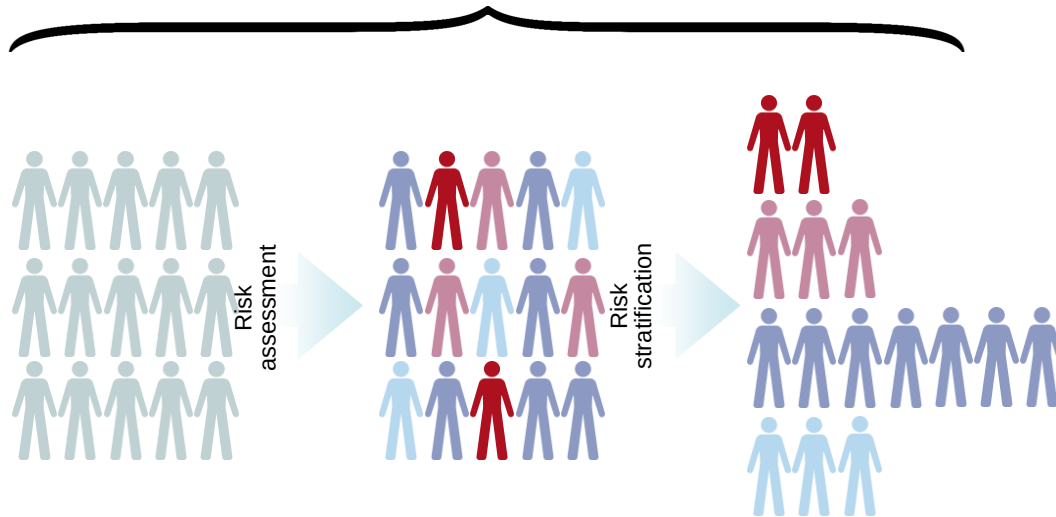
ELSI



Risk stratification in lung cancer screening

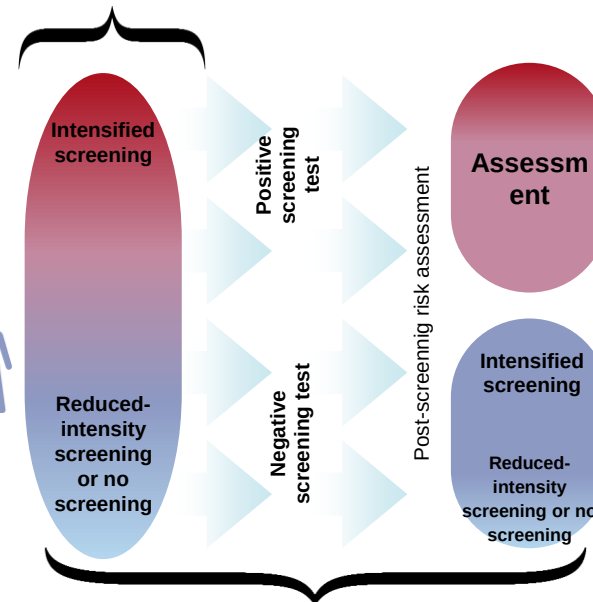
Who should be screened:

- Age
- Smoking history (model-based risk or pack/year threshold)
- Occupational exposure
- Other exposures
- Comorbidities



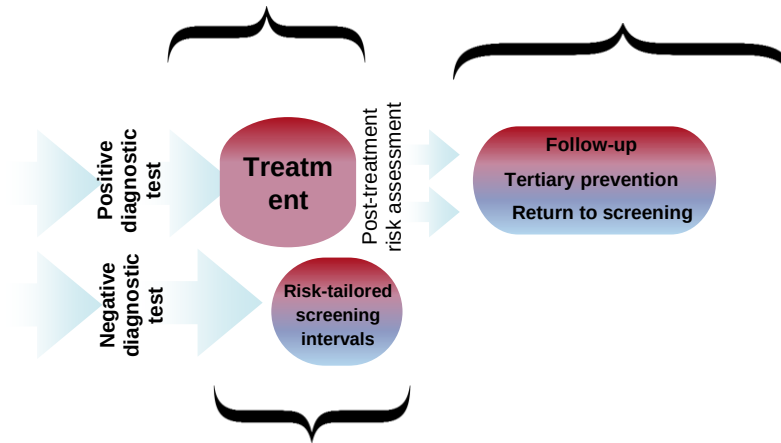
Triage of undetermined nodules:

- LDCT results
- Radiomics
- biomarkers



Treatment:

- Assessment results



Return to screening:

- Smoking history
- LDCT results
- Radiomics
- Biomarkers

Defining screening interval:

- Smoking history
- LDCT results
- Radiomics
- Biomarkers

Who should be screened?

- The eligibility for screening is defined by the risk.
 - Model-based
 - Pack/year-age based

PLCOM 2012 $\geq 1.7\%$ at 6y:

- SES
- BMI
- Family history
- COPD
- Other cancers
- Smoking history

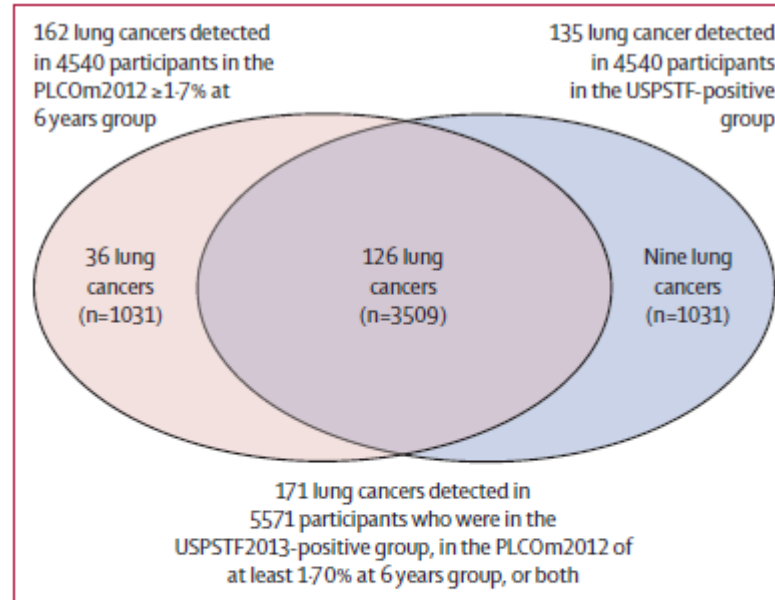


Figure: Venn diagram describing the distribution of individuals and lung cancer cases by criteria (USPSTF2013 positivity and PLCom2012 $\geq 1.7\%$ at 6 years status)

27 (15.8% [95% CI 10.7–22.1%]; $p < 0.0001$) of 171 more lung cancers were detected by PLCom2012 than USPSTF criteria. The figure excludes six lung cancers detected in 248 individuals who were USPSTF-negative but were enrolled because they had PLCom2012 risks at least 1.5% at 6 years and less than 1.70% at 6 years.

USPSTF 2013 criteria:

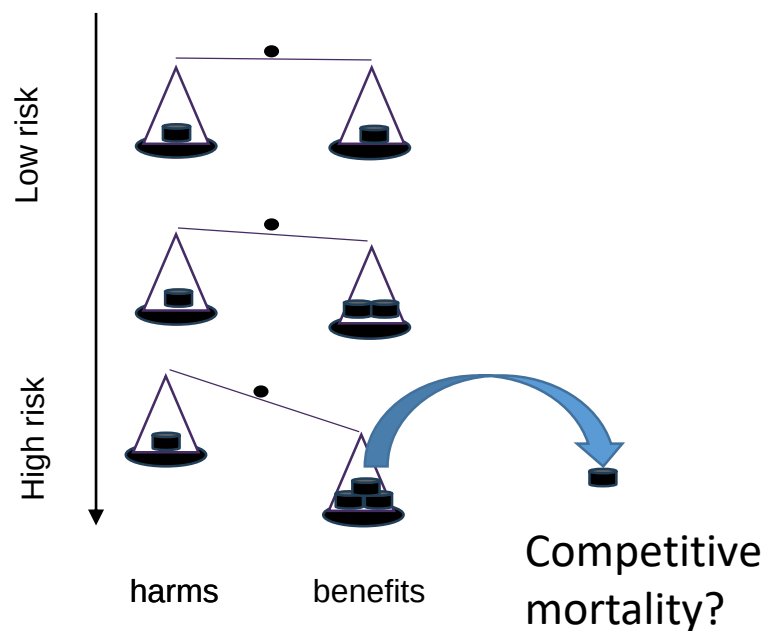
- age 55-80;
- >30 p/y;
- <15 quit

Who should be screened?

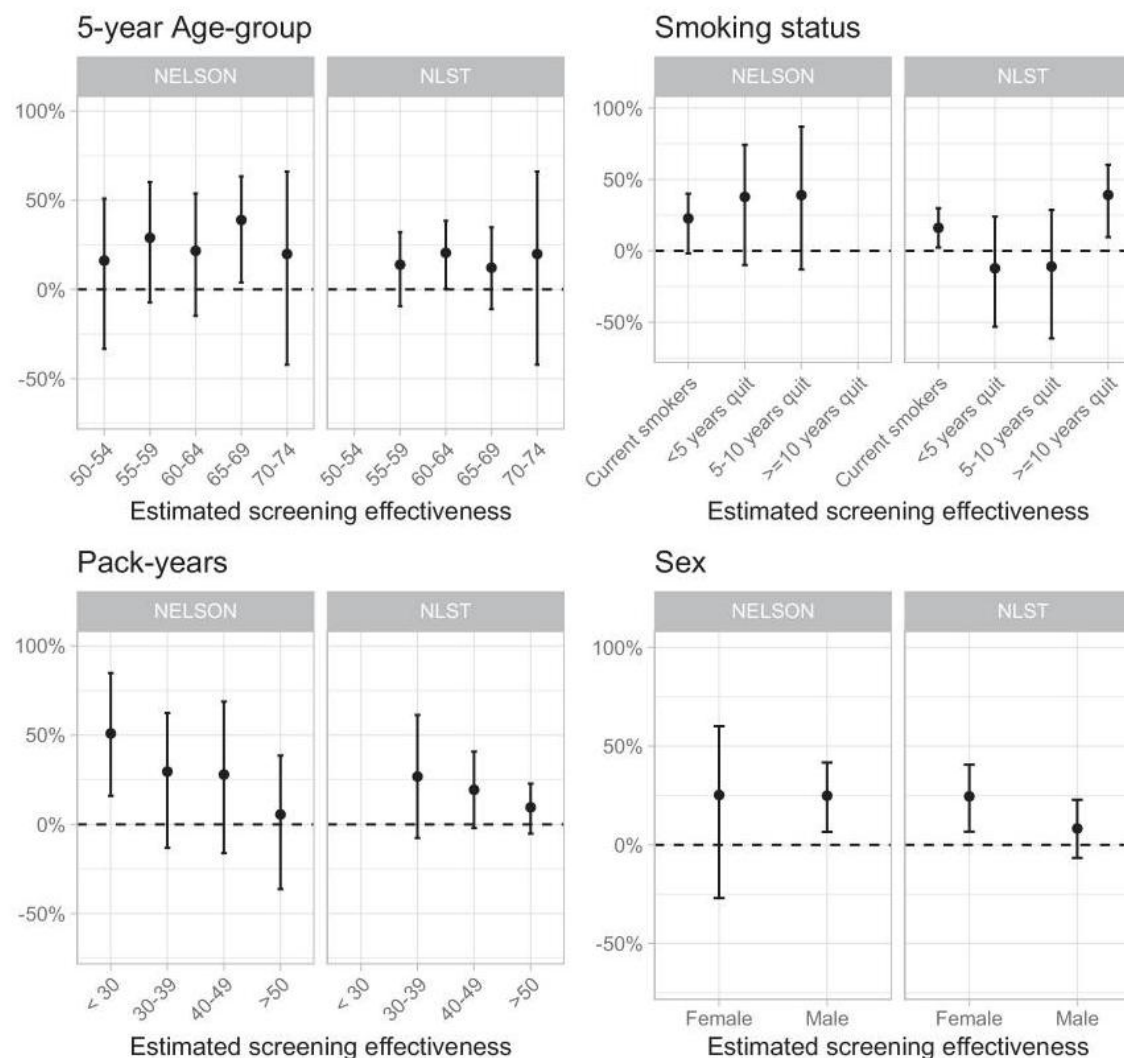


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- The higher the risk
the larger the
benefits? Maybe not!

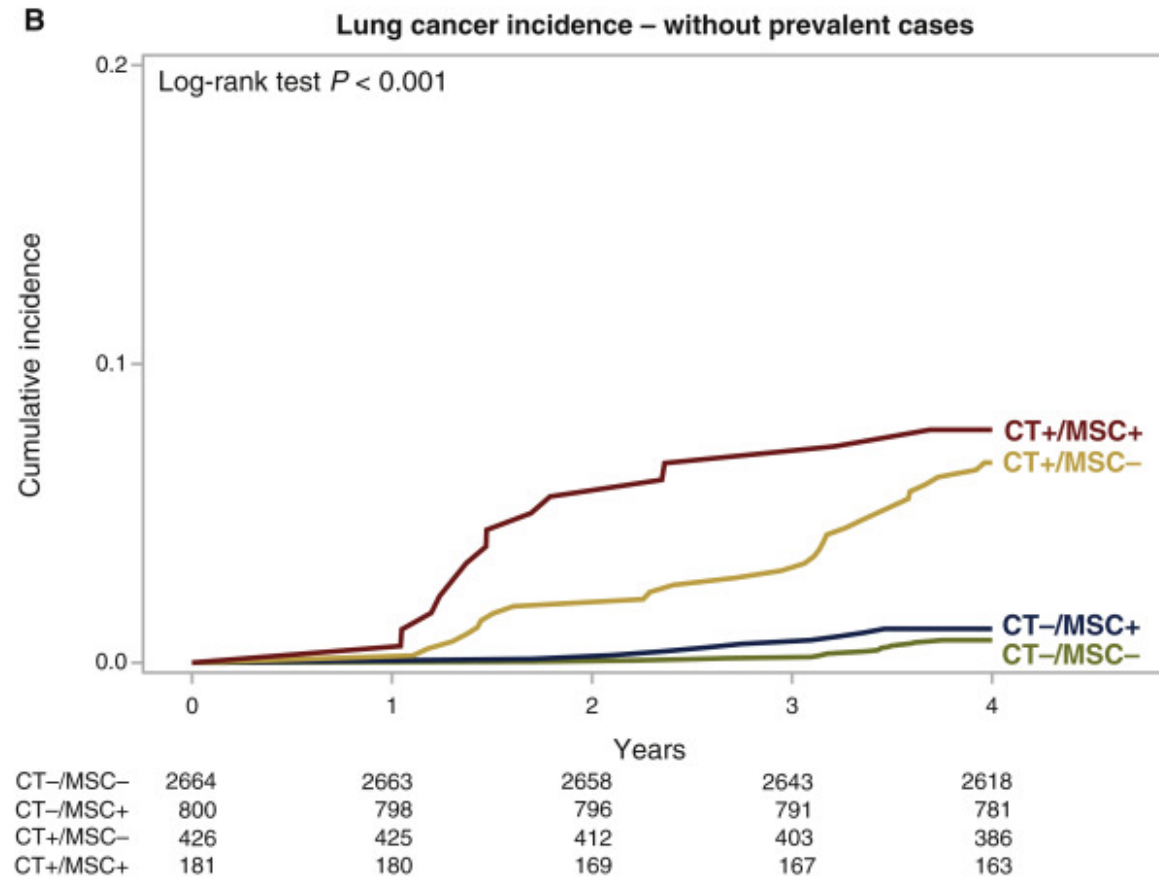
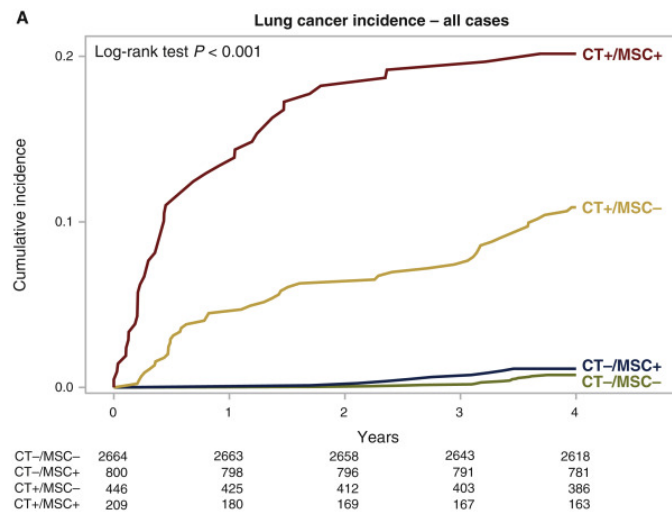


Screening effectiveness estimates for overall LC mortality, by risk-factor



Risk-based screening interval

Imaging and miRNA results may stratify the risk at two years.



New technologies in risk stratification

Table 2. Role of Emerging Tools to Enhance Lung Cancer Screening.^{*}

Tool	Select Target Population for Screening	Assist with Screening Uptake	Assist with Decision to Be Screened	Promote Adherence to Screening	Tailor Screening Interval	Assist with Lung Nodule Management	Assist with Capacity Issues
AI-assisted image reading	No	No	No	Yes	Yes	Yes	Yes
AI-assisted risk and nodule assessment	Yes	No	Yes	Yes	Yes	Yes	Yes
Education and health-promotion tools	Yes	Yes	Yes	Yes	No	No	No
Electronic medical record reminders and scheduling tools	No	Yes	No	Yes	No	Yes	No
Molecular biomarkers	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Population management and navigation tools†	No	Yes	Yes	Yes	No	Yes	Yes
Virtual shared decision-making tools	No	Yes	Yes	Yes	No	Yes	Yes

^{*} This table was compiled by the authors. "Yes" indicates that the given tool or tools can be used for the indicated role, whereas "No" indicates that the tool is not applicable to the task.

† Patient navigation (also called pathway navigation) is a process in which an appropriately trained representative, designated a navigator, proactively reaches out to provide individually tailored support to enable persons, particularly those encountering various types of disparities, to overcome barriers to access to health care services and pathways.

Risk stratification in prostate cancer screening

Who should be screened:

- Age
- Family history
- PSA value

Triage to MRI:

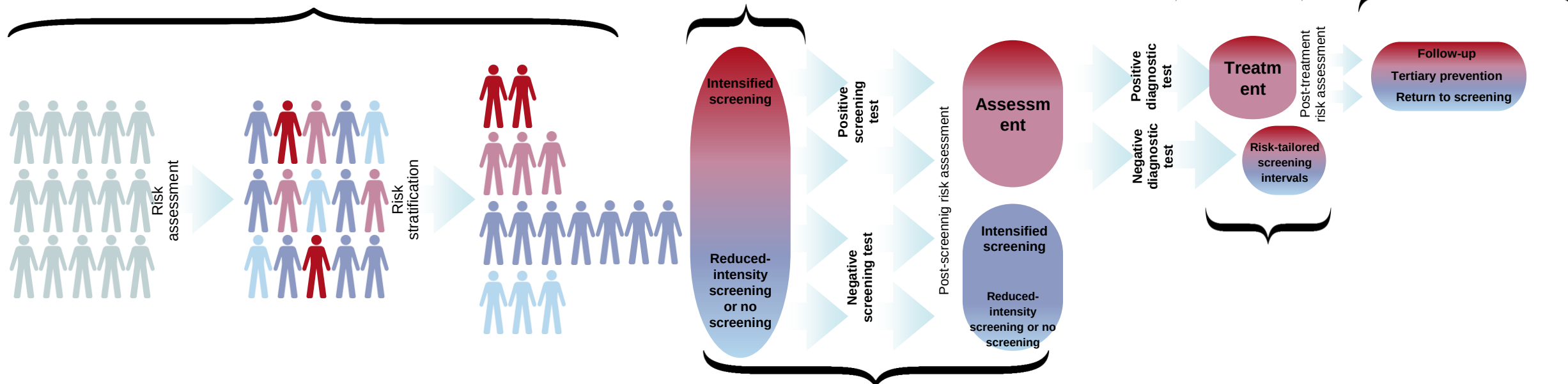
- PSA
- Biomarkers (ex. Stockholm 3)
- Clinical conditions

Triage to biopsy:

- PSA density
- MRI results
- Biomarkers

Treatment vs conservative:

- Gleason
- Comorbidities
- Imaging
- Radiomics



Defining screening interval:

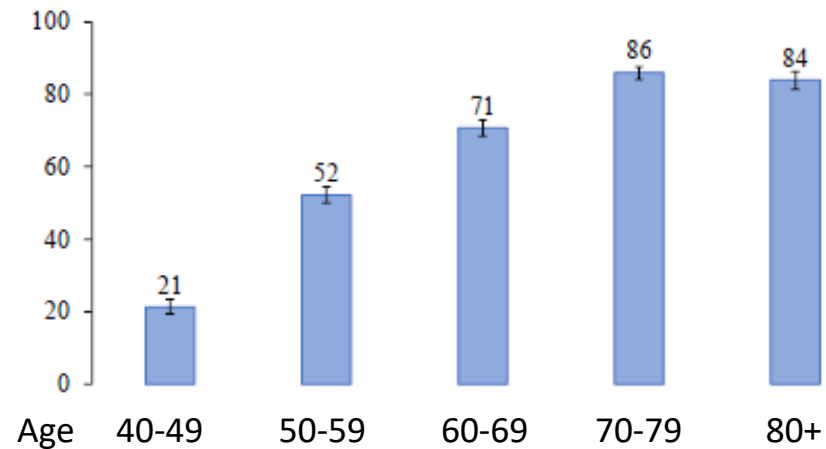
- PSA value
- Clinical conditions

EC recommendation: a focus on appropriateness

«Considering the preliminary evidence and the significant amount of ongoing opportunistic screening, countries should consider a stepwise approach, including piloting and further research, to evaluate the feasibility and effectiveness of the implementation of organised programmes aimed at ensuring appropriate management and quality on the basis of prostate-specific antigen (PSA) testing for men, in combination with additional magnetic resonance imaging (MRI) scanning as a follow-up test.»

Who should be screened?

Prevalence of men who had at least one PSA test in their life, by age, Italy 2025



Can we use spontaneous screening to inform who should be screened?

TABLE 4 Clinically significant prostate cancer (EAU risk group other than low risk) (csPCa) cases and cumulative incidence by duration of follow-up and baseline PSA level

Follow-up time (years)	Cumulative number of csPCa cases and cumulative csPCa incidence by EAU risk		
	<1 ng/mL	1-1.99 ng/mL	2-2.99 ng/mL
2	1 (0.01%)	4 (0.06%)	3 (0.12%)
4	3 (0.03%)	21 (0.3%)	29 (1.14%)
6	8 (0.07%)	44 (0.6%)	93 (3.7%)
8	18 (0.17%)	95 (1.4%)	139 (5.5%)
10	49 (0.5%)	188 (2.7%)	193 (7.6%)

Ola et al. Int J Cancer, 2023

How should we screen? PRAISE-U protocol



Figure 1 Pathway for risk stratified prostate cancer screening

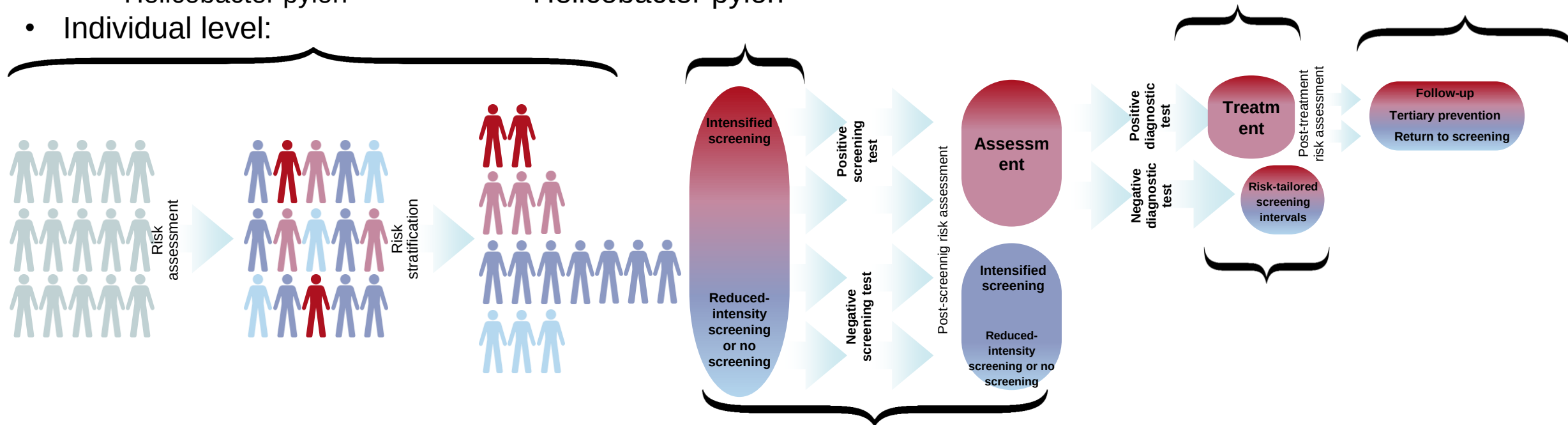
Risk stratification in gastric cancer screening (to be completed)

Who should be screened:

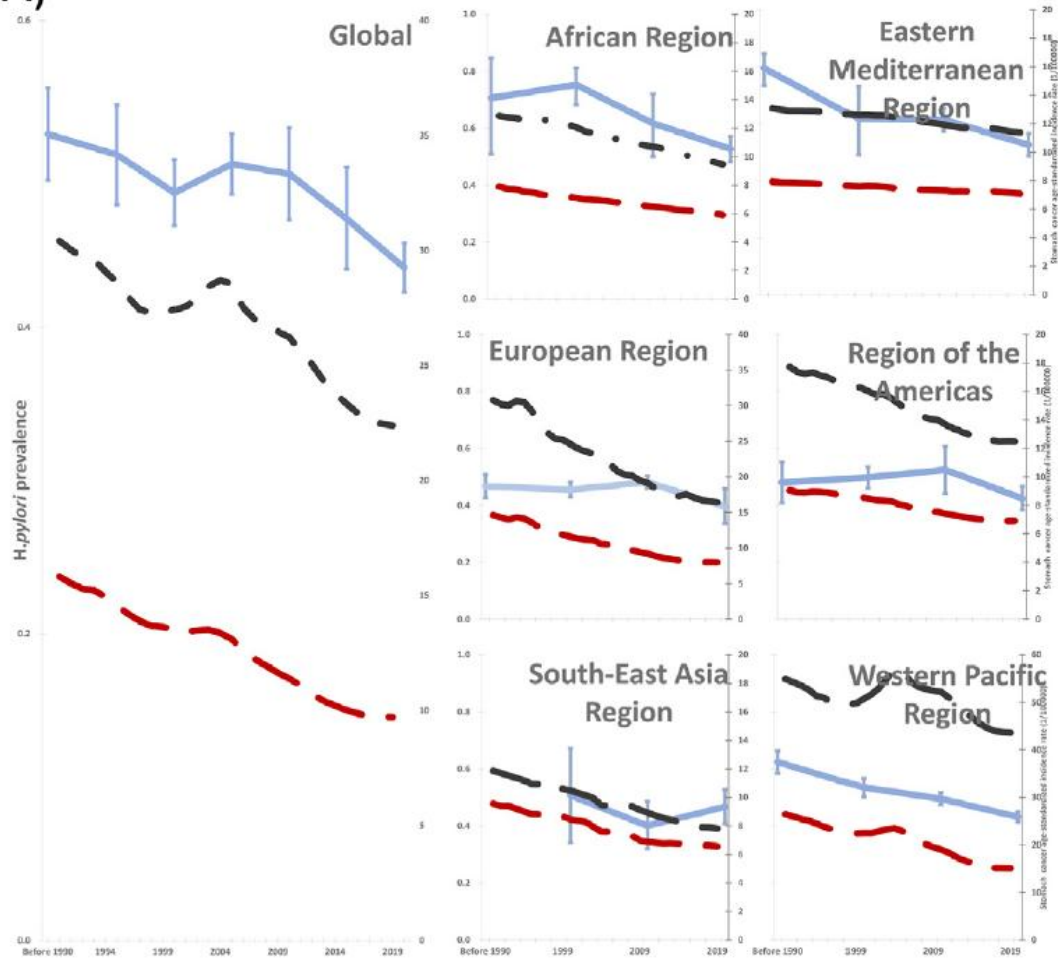
- Population level:
 - Incidence of GC by age and cohort
 - Prevalence of *Helicobacter pylori*
- Individual level:

How should be screened:

- Prevalence of preclinical GC
- Prevalence of *Helicobacter pylori*



(A)



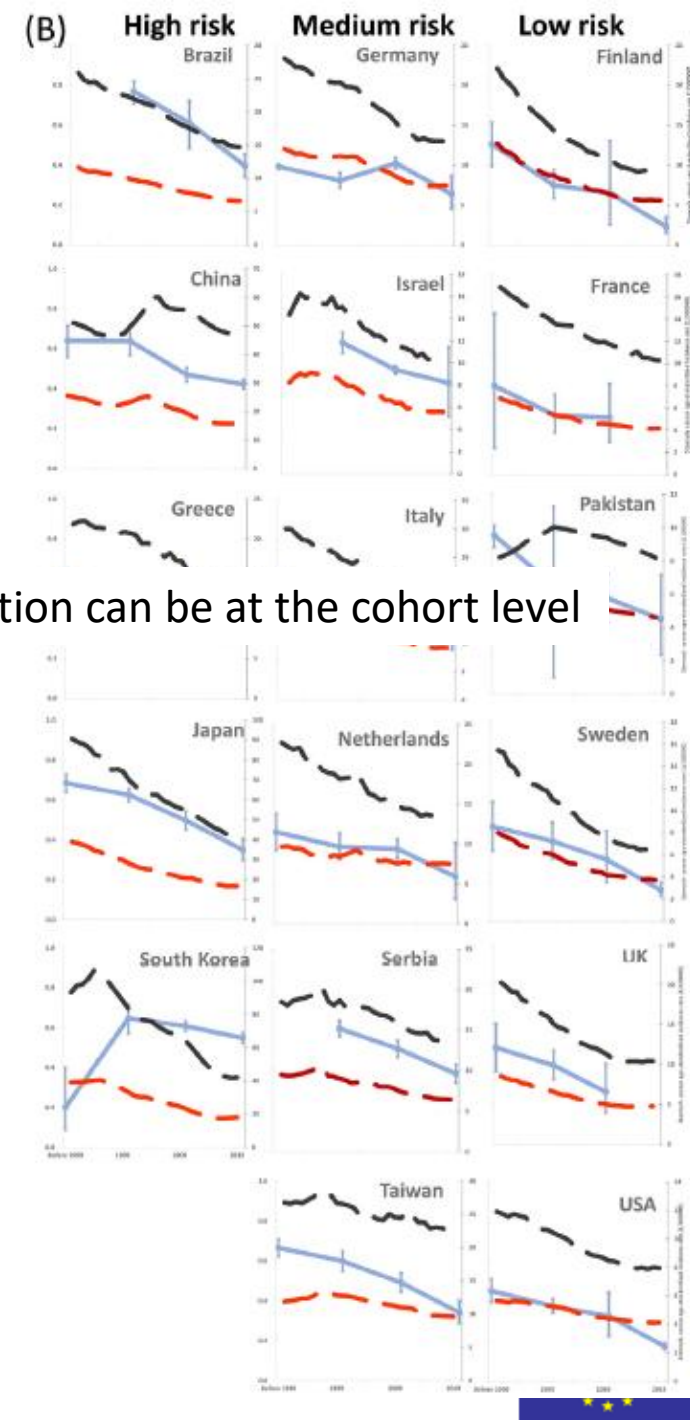
— Estimated adults HP prevalence

— Gastric cancer incidence rate (male)

— Gastric cancer incidence rate (female)

Chen et al. Gastroenterology 2024

(B)



Risk-stratification can be at the cohort level

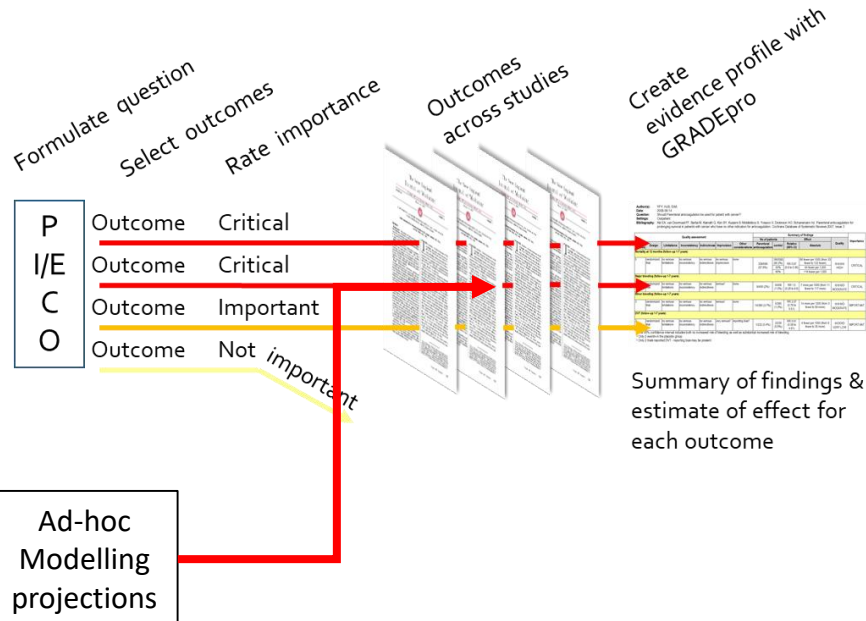
We have a recent example of risk stratification at the cohort level

- The cohorts of girls vaccinated for HPV are now reaching the age of screening
- They have almost no risk of HPV16 and 18 infection and consequently low risk of cervical cancer (particularly of early-onset cervical cancer)
- How to screen these women was one of the questions afforded by the EC-CvC initiative

Question: Optimal age to start and appropriate screening interval?



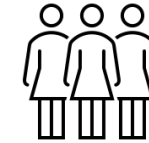
European Health and Digital Executive Agency (HADEA) 2023-2026 [EU4Health grant agreement No 101122251]



Is it feasible to invite differently based on individual vaccination status?

Yes

What would be the optimal age to start and appropriate interval for HPV-based screening in **fully vaccinated individuals with cervix**?



Unvaccinated individuals with cervix

Modelling results to support screening indications in

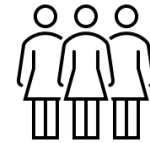


fully vaccinated individuals with cervix

No

What would be the optimal age to start and appropriate interval for HPV-based screening in a **highly vaccinated cohort**?

Modelling results to support screening indications in



Unvaccinated individuals with cervix



Highly vaccinated cohorts



fully vaccinated individuals with cervix

0%

100%

EC-CvC Recommendations for HPV-vaccinated birth cohorts (March 2026)

	Age to start	Interval
Vaccinated women (individually assessed)	30 yo	10 years
Vaccine coverage >75%	30 yo	10 years
Vaccine coverage 50% to 74%, pre-vaccination HPV16 risk low (<6% in the age 25-29)	30 yo	10 years
Vaccine coverage 50% to 74%, pre-vaccination HPV16 risk low (≥6% in the age 25-29)	25 yo	10 years
Vaccine coverage <50%	25yo	5 to 7 years

- Coverage measured at the age of 15, with any vaccine, both gender neutral or girls only.
- Instead of coverage and pre-vaccination HPV16 prevalence, the residual risk in the cohort can be assessed directly by the post-vaccination HPV16 prevalence at 25:
 - <0.3%: start at 30, 10 year interval
 - <1%: start 25, 10 year interval
 - >1%: start 25, 5 to 7 year interval

Some open issues

- When do we need a trial to demonstrate that risk-stratified screening is superior to age-based screening?
- What can a trial test? A proof of principle or a specific risk-assessment/thresholds/management protocol?
- How can threshold/management couples be determined?
- How can we define the thresholds taking into account evidence and values?

Conclusions

- Risk stratification implies identifying people at higher and lower risk of cancer
- We must adapt screening protocols to both cases; this means also reducing intensity in those at lower risk.
- Examples as the prostate cancer screening, where harms are more evident, may help increasing the acceptance of de-scaling...



Thank you for your attention
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