Modelling for prostate cancer screening to assess the cost-effectiveness

Shuang Hao, Health Economist

Department of Medical Epidemiology and Biostatistics (MEB)
Karolinska Institutet
2023-03-30

About me

- Health economist who recently defended my PhD thesis (2022)
- “Prostate cancer testing in Sweden: the interplay between cost and effectiveness”
- Research interests: health economic evaluations of cancer screening, diagnosis and treatment
- Consultant at the Stockholm Centre for Health Economics (StoCHE), Region Stockholm
- PhD Health Economics, MPH Health Economics, MSc Applied Economics, BSc Statistics
- 9-year work experience in the consulting and pharmaceutical industry

Agenda

The way health economists do things: trial-based vs. lifetime

Modelling approach: Markov vs. individual-based simulations

Per-protocol vs. intention-to-treat: implications for modelling

Sensitivity analyses: one-way vs. probabilistic

Agenda

The way health economists do things: trial-based vs. lifetime

Modelling approach: Markov vs. individual-based simulations

Per-protocol vs. intention-to-treat: implications for modelling

Sensitivity analyses: one-way vs. probabilistic

Types of economic evaluation

Economic evaluation	Health consequences
CUA Cost-utility analysis	QALYs (quality-adjusted life years) Generic or disease specific outcome measures ("utilities")
CEA Cost-effectiveness analysis	A single, common effect that may differ in magnitude; e.g. case detected
CBA Cost-benefit analysis	Translate effects into monetary benefits; e.g. translate disability days avoided, life-years or QALYs gained

Advantage of using QALYs

Simultaneously capture gains from
- reduced morbidity
- reduced mortality

Integrate these into a single measure

Source: Drummond (2015)

Costs

Perspective	Direct	Indirect
Healthcare	Costs for testing, diagnosis and managing the disease	N/A
Societal	• Direct healthcare • Non-healthcare, e.g. transportation, social services, informal care*	Productivity losses • Morbidity: short- and long-term sick leave, early retirement • Premature mortality

Primary: Healthcare

Societal perspective may discriminate against those who are not in the labour market: children, disabled, unemployed, elderly

* Informal care is debatable. It is sometimes considered as indirect costs.

Cost-utility analysis

Comparisons

Costs (C_1)

QALYs (E_1)

vs.

Costs (C_0)

QALYs (E_0)

Incremental cost-effectiveness ratio (ICER)

$$\text{ICER} = \frac{\Delta C}{\Delta E} = \frac{C_1 - C_0}{E_1 - E_0}$$

Cost-effectiveness threshold
(willingness-to-pay)

Category	Costs per QALY gained
Low	<100,000 SEK
Moderate	100,000 (incl.) – 500,000 SEK
High	500,000 (incl.) – 1,000,000 SEK
Very high	≥1,000,000 SEK

Trial-based vs. Lifetime

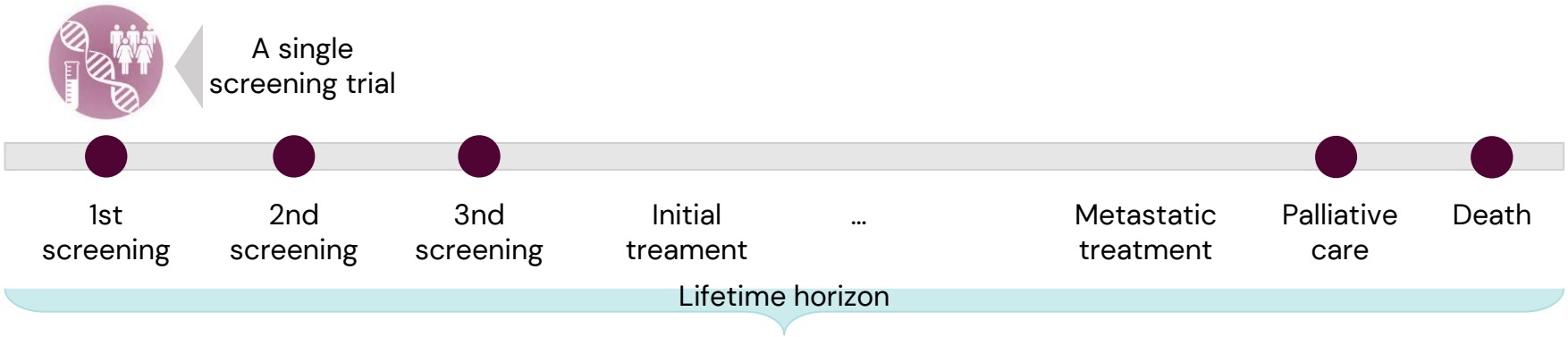
A single screening trial

What would happen in the long run?

1st screening

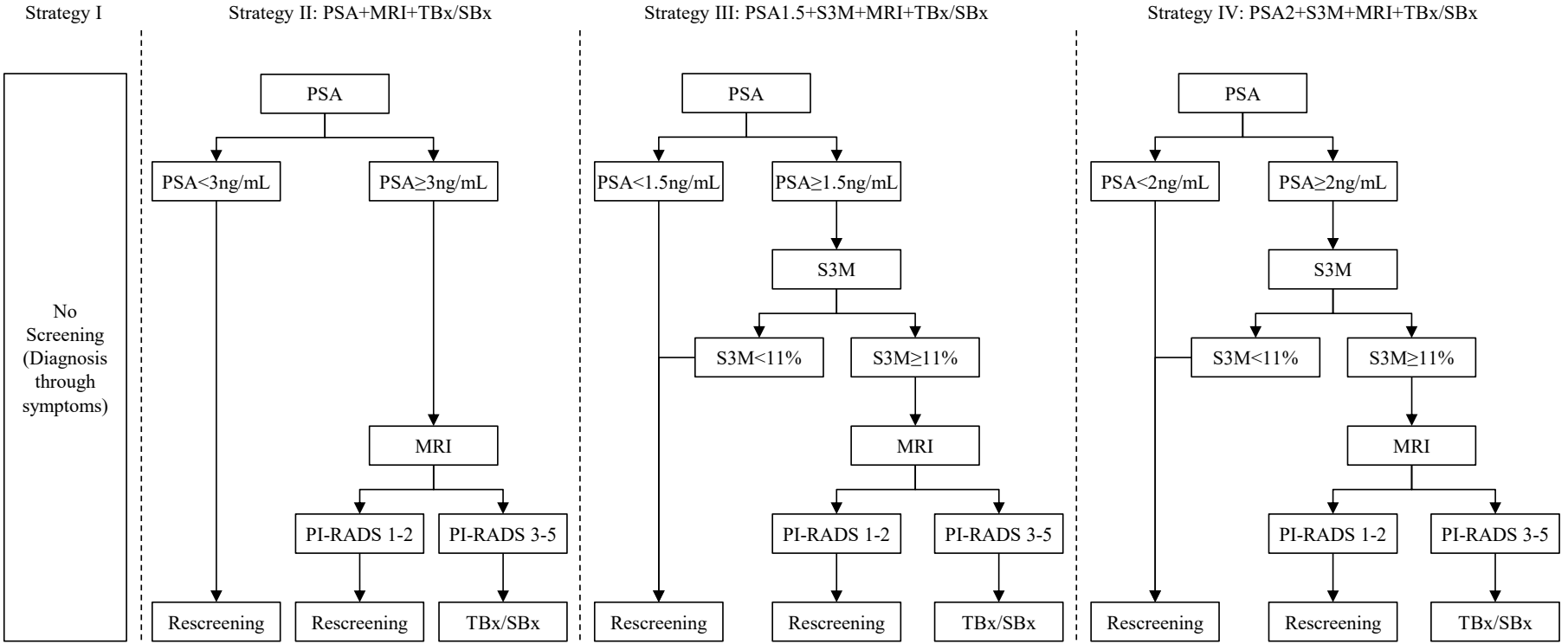
- Easy to compare screening strategies with no screening or current testing practice
- Straightforward to calculate the health consequences and costs
- Focus on shorter-term effects rather than effects after the trial period

Trial-based vs. Lifetime



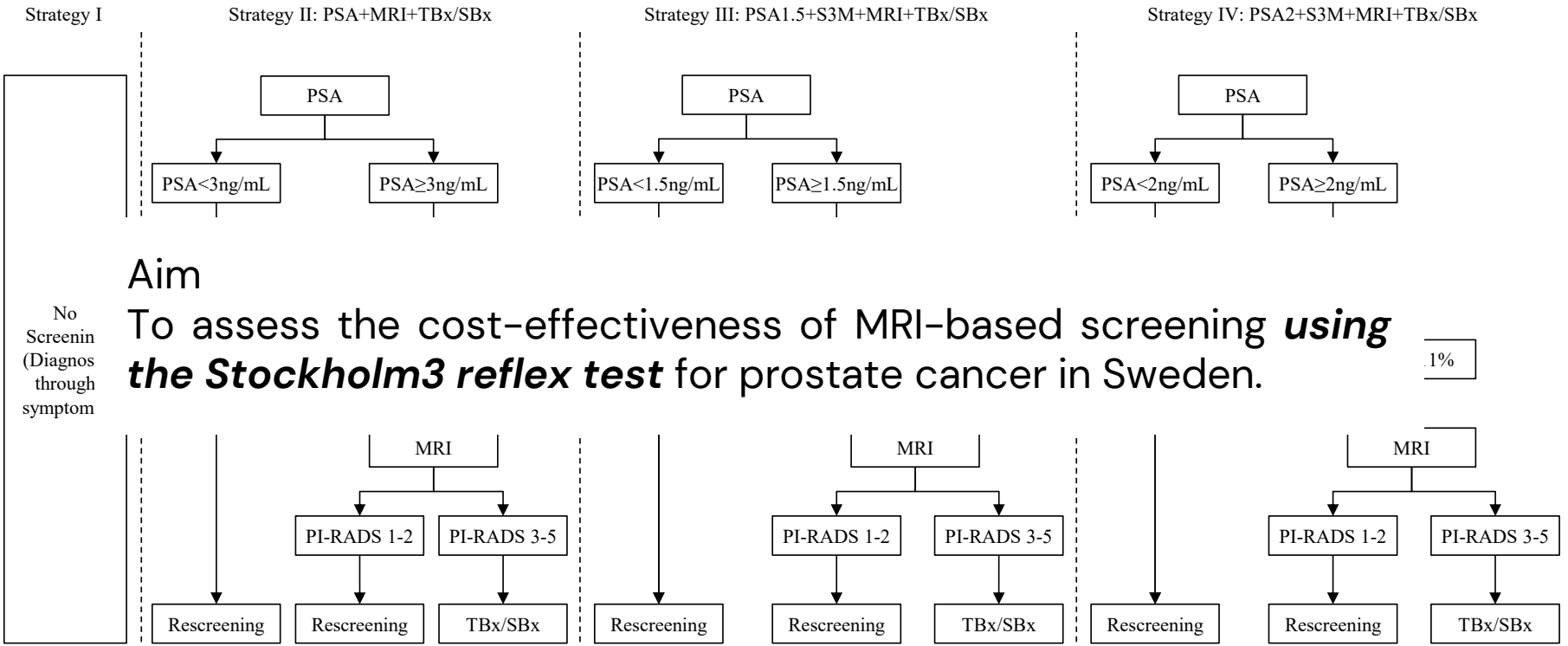
- Captures the long-term health consequences and costs
- More applicable to health interventions that will affect survival
- Encounter challenges in how to capture the long-term effects
  - Lack of evidence
  - Difficult to model

Research question



MRI: magnetic resonance imaging; PI-RADS: Prostate Imaging Reporting and Data System; PSA: prostate-specific antigen; SBx: systematic biopsy; TBx: MRI-guided targeted biopsy

Research question



MRI: magnetic resonance imaging; PI-RADS: Prostate Imaging Reporting and Data System; PSA: prostate-specific antigen; SBx: systematic biopsy; TBx: MRI-guided targeted biopsy

Agenda

The way health economists do things: trial-based vs. lifetime

Modelling approach: Markov vs. individual-based simulations

Per-protocol vs. intention-to-treat: implications for modelling

Sensitivity analyses: one-way vs. probabilistic

Overview of health economic models

1. Aggregate, branch-based, discrete time: Decision tree
2. Aggregate, state-based, discrete time, clock-forward: Markov
3. Aggregate, state-based, continuous time, clock-forward: Markov
4. Aggregate, state-based, continuous time, clock-reset: semi-Markov
5. Individual, state-based + attribute-based, continuous time, mixed time scales: Microsimulation or Discrete Event Simulation (DES)

Credit: Mark Clements' talk Model taxonomy for HTA on 2022-06-14

Why microsimulation?

Using individual-level data to address individual heterogeneity

- Available longitudinal data
- Ability to account for individual heterogeneity within the population of interest

State transition intensities depend on a patient's history

- Incorporate the memory of events occurring for simulated individuals in the model e.g. time since disease onset, the occurrence of previous events, or time-varying response to treatment
- Also supports individualised screening interventions

Flexible distributions for event times

Bring evidence from specific RCTs together with data from other sources

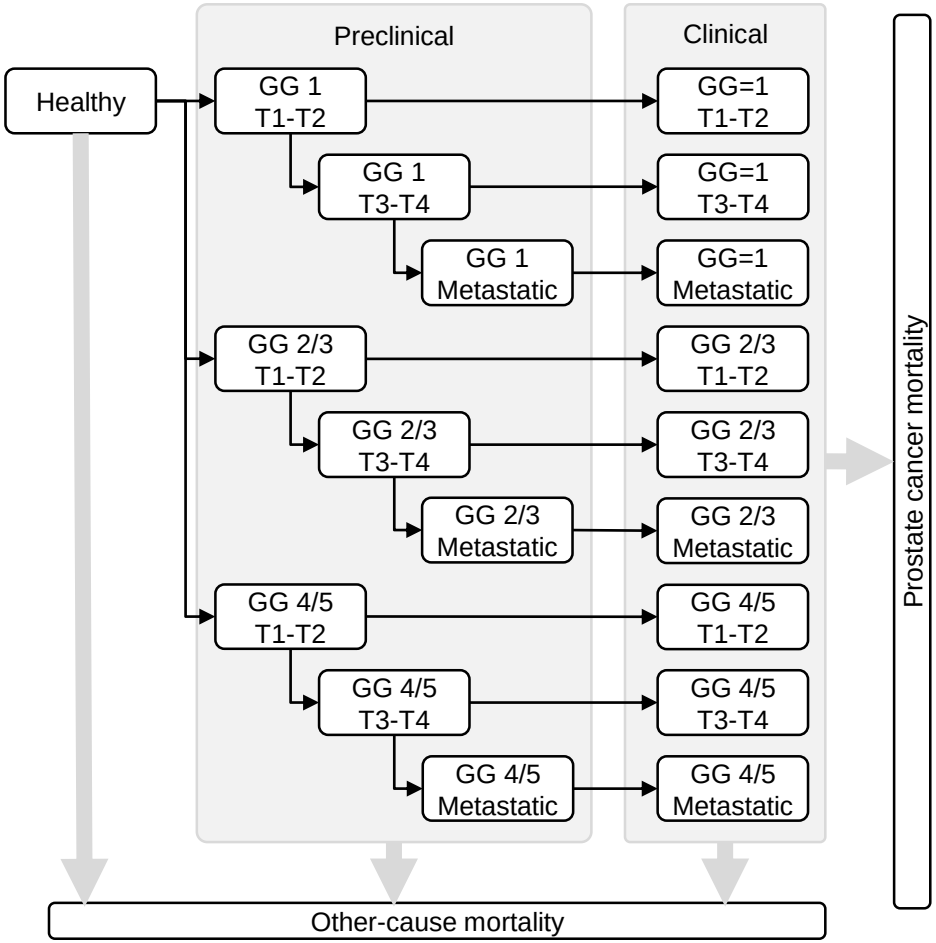
Difficulties in using microsimulation

- Complexity
- “Black box”, less transparent
- Data availability
- High computational workload (for multi-core simulations in R and C++, see our microsimulation package on CRAN)
- Monte Carlo uncertainty for individual-based simulations

Microsimulation model

The Prostata microsimulation model

- Simulated individual life histories from disease onset, disease progression through to deaths
- Included a longitudinal PSA sub-model (same as FHCRC), T-stage, M-stage and ISUP Grade Group
- Validated and well calibrated for Sweden and ERSPC
- Supports reliable health economic evaluations of cancer screening
- Open access to the model (github.com/mclements/prostate)



Agenda

The way health economists do things: trial-based vs. lifetime

Modelling approach: Markov vs. individual-based simulations

Per-protocol vs. intention-to-treat: implications for modelling

Sensitivity analyses: one-way vs. probabilistic

Per-protocol vs. Intention-to-treat

	Intention-to-treat	Per-protocol
Principal	As randomised, ignoring the actual test or treatment received	As randomised, conditional on protocol compliance
Scope	**Effectiveness** of the test or treatment	**Efficacy** of the test or treatment under ideal circumstances (compliance)
Strengths	Randomisation – protected from bias due to imbalance of baseline characteristics	Proof of the diagnostic or therapeutic concept; **more direct for modelling**
Limitations	• Missing data: imputation required • Generalisability: difference in compliance between the study and real-life	• Power: may be reduced • Violation of randomisation: selection bias • May over-estimate the effect and does not represent the real-life situation

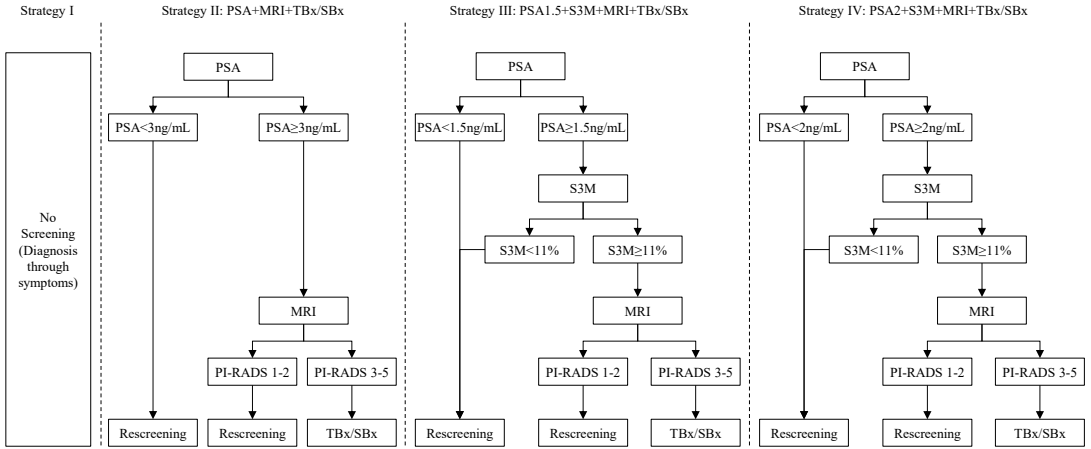
Primary choice in modelling for prostate cancer screening: per-protocol

- Issues with generalisability of ITT
- Uncertainties in screening compliance (participation) and biopsy compliance: captured as parameters in the model
- Address reduced power: model-based multiple imputation (assuming missing at random given other covariates)

- Example: two-arm diagnostic trial (standard biopsy vs MRI-first and then biopsy), with poor biopsy compliance in the standard arm

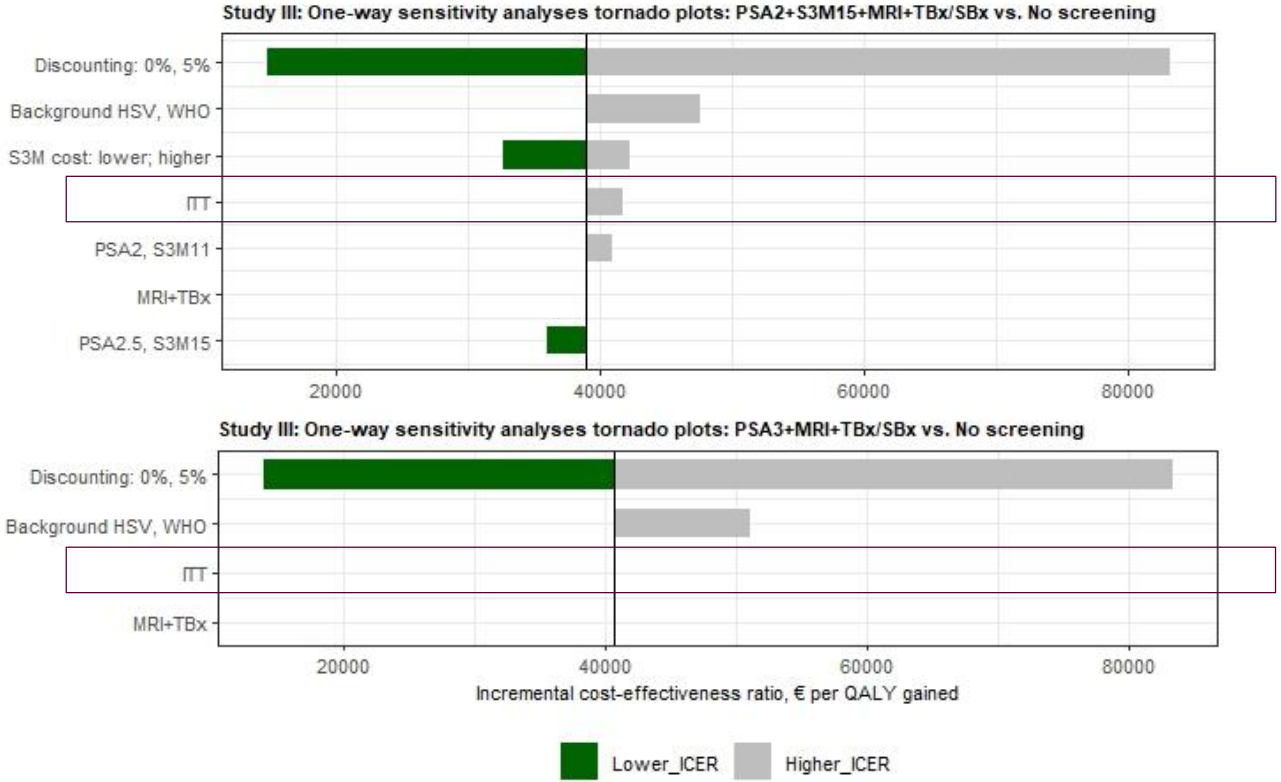
Differences in the test performance using PP and ITT

Test characteristics	PP	95% CI (PP)	ITT	95% CI (ITT)
Pr(MRI+|PSA+, GG=0, MRI+TBx/SBx)	0.148	(0.126, 0.192)	0.150	(0.129, 0.195)
Pr(MRI+|PSA≥1.5, S3M≥15%, GG=0, MRI+TBx/SBx)	0.167	(0.124, 0.224)	0.175	(0.131, 0.233)
Pr(MRI+|PSA≥2, S3M≥15%, GG=0, MRI+TBx/SBx)	0.164	(0.119, 0.226)	0.174	(0.127, 0.236)



MRI: magnetic resonance imaging; PI-RADS: Prostate Imaging Reporting and Data System; PSA: prostate-specific antigen; SBx: systematic biopsy; TBx: MRI-guided targeted biopsy

Differences in the results using PP and ITT



+7.2%

+0.2%

HSV: health state value; ITT: intention-to-treat; MRI: magnetic resonance imaging; PSA: prostate-specific antigen; QALY: quality-adjust life-year; S3M: Stockholm3 test; TBx: targeted biopsy; TBx/SBx: the combined targeted and systematic biopsy; WHO: World Health Organisation

Agenda

The way health economists do things: trial-based vs. lifetime

Modelling approach: Markov vs. individual-based simulations

Per-protocol vs. intention-to-treat: implications for modelling

Sensitivity analyses: one-way vs. probabilistic

Both one-way and probabilistic sensitivity analyses are important

One-way: how a system is sensitive to key parameters

- Costs, utilities, discount rate
- Screening: age, screening interval, test threshold, trial evidence using PP or ITT, biopsy procedures, etc.

Probabilistic: addresses joint uncertainties

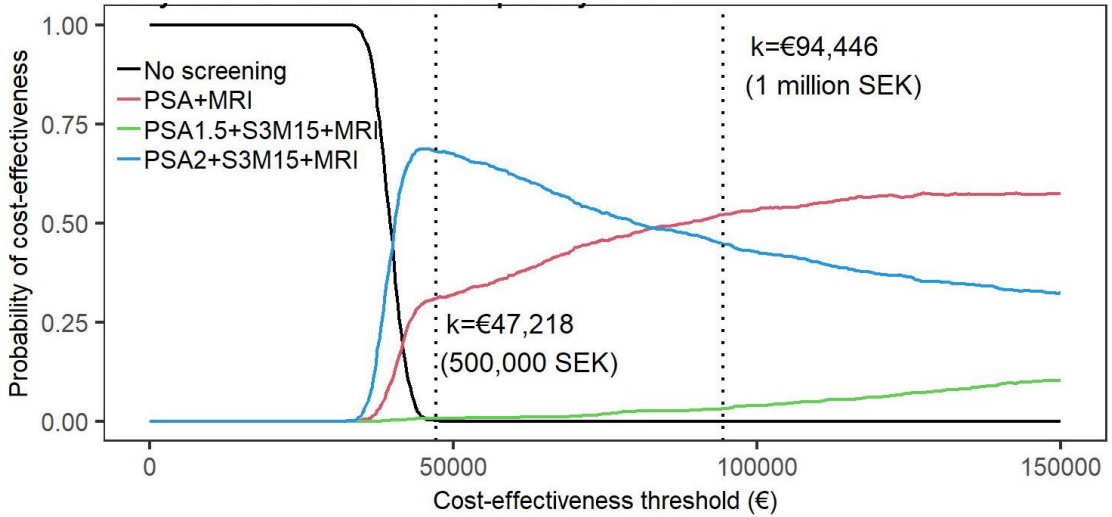
- Parametric bootstrap or Bayesian analysis
- May assume parameter independence
- Cost-effectiveness plane, cost-effectiveness acceptability curve (CEAC), etc.
- Screening: test performance, costs, utilities

- Both are required by the Swedish guidelines for assessing cost-effectiveness
- Not necessarily required by guidelines from other countries

Mathematically, for CEAC

- $E_\theta(Y \mid \theta)$ vs. $Y(E_\theta(\theta))$ where θ are the parameters (as a distribution) and Y could be costs or effects. Different countries accept one or both of these approaches
- $CEAC_k$ = Pr (Strategy k is cost effective | θ, τ), where τ is the cost-effectiveness threshold (willingness-to-pay threshold)

Cost-effectiveness acceptability curve (CEAC)



At a nominal threshold of €47,218 per QALY gained

- Blue: 70% probability of being cost-effective

At a nominal threshold of €83,000 per QALY gained

- Blue & red: equal probability of being cost-effective

At a nominal threshold of €94,446 per QALY gained

- Red: more than 50% probability of being cost-effective compared with other strategies

Summary

- Health economics is an important component for translating epidemiological findings into policy
- Health economics needs good modelling – which is potentially a nice fit for biostatisticians ☺
  - Long-term predictions outside of the observed data
  - Modelling for the disease natural history (e.g. using joint models)


KAROLINSKA INSTITUTET
ANNO 1810
Karolinska
Institutet