Cost-effectiveness for prostate cancer testing: bridging disciplines

Mark Clements

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Background

- Prostate cancer is the most common cause of cancer death for Swedish males
- 1 in 50 Swedish males are living with a prostate cancer diagnosis
- Prostate-specific antigen (PSA) test is an inexpensive and common prostate cancer screening test
- European Random Study of Prostate Cancer predicted a 20% reduction in prostate cancer mortality over 16 years due to PSA testing
- The harms from PSA testing may outweigh the benefits from early detection
- How can we better plan for prostate cancer testing?

Policy context: OPT

- The Regional Cancer Centres have a document entitled "Rekommendationer om organiserad prostatacancer-testning (OPT)"
- This provides a road-map to investigate organised approaches to reduce the harms from prostate cancer testing
- Interventions could include:
  - Magnetic resonance imaging (MRI), which allows many men with a positive PSA test and no cancer to avoid a biopsy
  - MRI-targeted biopsies may complement (or replace) systematic biopsies
  - New reflex screening tests (e.g. Stockholm3, 4K Score, PHI) have better test characteristics, but they are costly

Stockholm3 test

- The Stockholm3 test includes a combination of clinical information, protein measurements (including PSA), and a genetic score based on single-nucleotide polymorphisms to estimate risk. It would be used as a reflex test after a PSA test (e.g. PSA $\geq$ 1.5 ng/mL).
- The STHLM3 trial assessed Stockholm3 in the context of systematic biopsies (Grönberg et al, 2015, Lancet Oncology)
- The STHLM3-MRI trial assessed Stockholm3 in the context of MRI and combined systematic/targeted biopsies (Nordström et al, 2021, Lancet Oncology)

Pepe et al. Phases of biomarker development for early detection of cancer. JNCI 2001;93:1054–1061.

Preclinical exploration	Phase 1	Promising directions identified
Clinical assay and validation	Phase 2	Clinical assay detects clinical disease
Retrospective longitudinal	Phase 3	Biomarker detects disease early before it becomes clinical and a *screen positive* rule is defined
Prospective screening	Phase 4	Extent and characteristics of disease detected by the test and the false referral rate are identified
Cancer control	Phase 5	Impact of screening on reducing the burden of disease on the population is identified

Development and effectiveness evaluation of the Stockholm3 test (Phases 1-4; Grönberg et al, 2015; Nordström et al, 2021)

Basic biology: candidate biomarkers (Phases 1 and 2)

Epidemiology: diagnostic trials (Phases 3 and 4)

Clinical context: screening and diagnostics

  Pathology: biopsies

Biostatistics: prediction and evaluation (and missing data)

Natural history model for prostate cancer (Phase 5; Karlsson et al, 2019, PLOS ONE)

Basic biology: how longitudinal PSA values relate to prostate cancer

Mathematical modelling: concise, predictive representation of the biology

Epidemiology: study design and data collection to estimate the parameters for the mathematical model

Biostatistics: estimating those parameters

Simulation: tools to implement, calibrate and validate the mathematical model

Cost-effectiveness evaluation of the S3M test (Phase 5)

Epidemiology: study design and data collection to represent the transitions between the states

Health economics: how to evaluate the evidence for cost-effectiveness, including uncertainty

- Costs for all of the screening and downstream states (Hao et al, 2020, BMC Health Services Research)
- Health state values (utilities) for all of the screening and downstream states (meta-analysis)

Both of these approaches make extensive use of the Stockholm PSA and Biopsy Register

Review of cost-effectiveness analysis

- We simulate for $n = 10^7$ individuals
- We calculate the life-time discounted quality-adjusted life-years (QALYs) and costs for a strategy k
- Let $U_{ki}(t)$ be the (cumulative) utilities for individual i at time t. Then

$$E(QALY_k) = \frac{1}{n} \sum_{i=1}^{n} \int_0^\infty \frac{dU_{ki}(t)}{(1+\delta)^t}$$

- Let $C_{ki}(t)$ be the (cumulative) costs for individual i at time t. Then

$$E(Costs_k) = \frac{1}{n} \sum_{i=1}^{n} \int_0^\infty \frac{dC_{ki}(t)}{(1+\delta)^t}$$

where δ is the discount rate (e.g. δ=0.03).

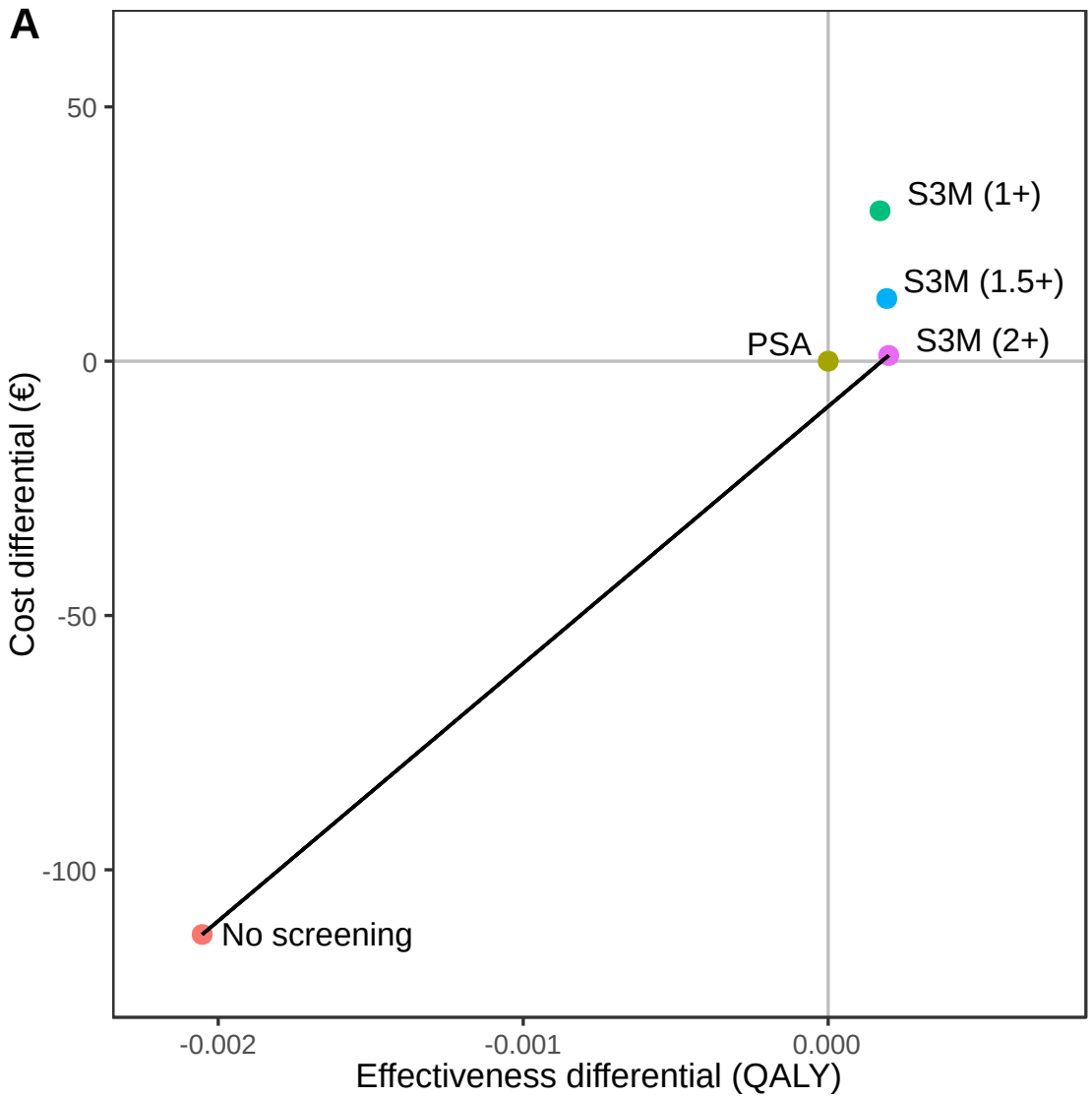
Review of cost-effectiveness analysis

- For a given willingness-to-pay threshold τ (e.g. €50,000 per QALY gained), we can calculate the net monetary benefit NMB_k as

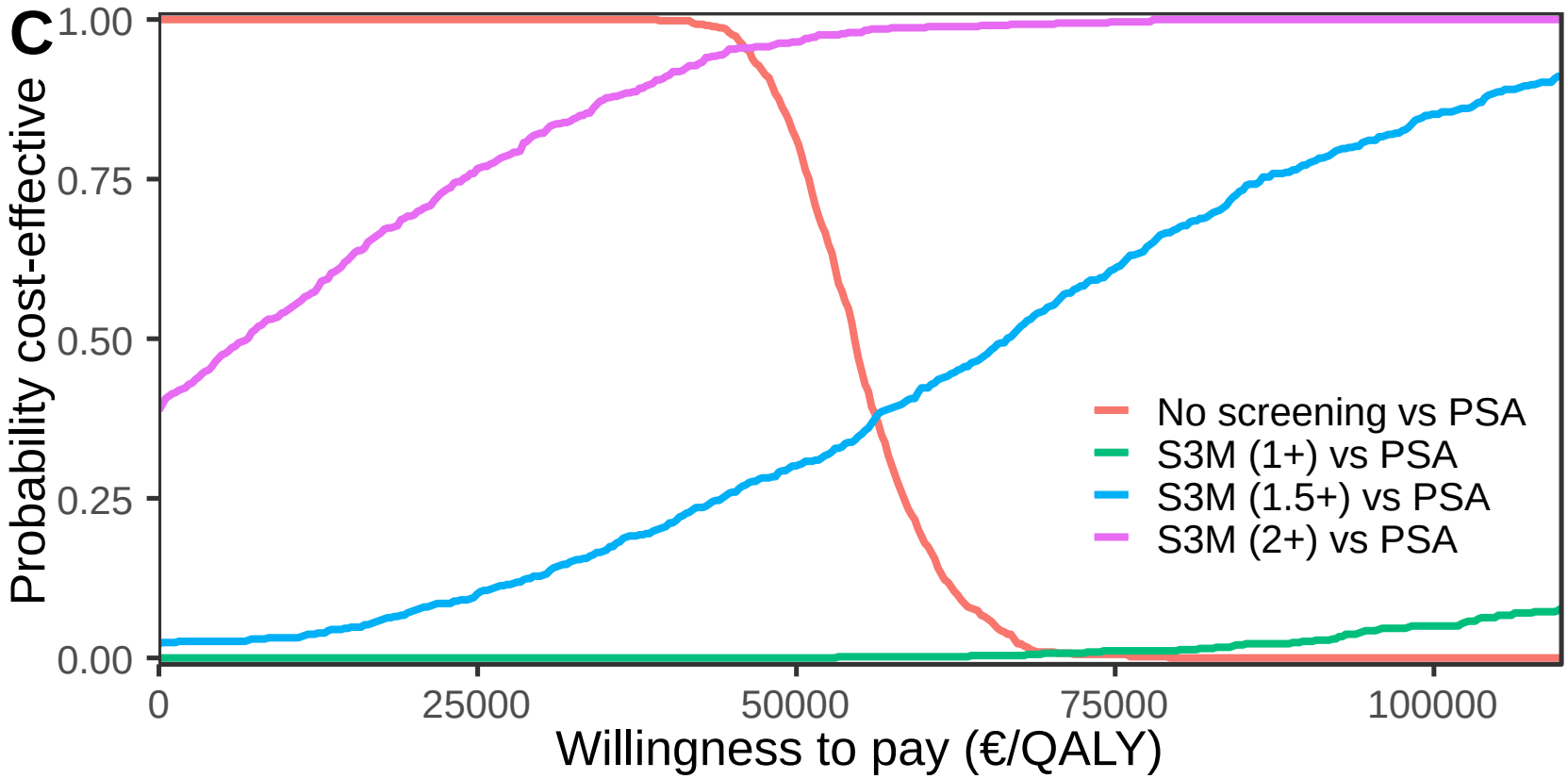
$$NMB_k = \tau\, E(QALY_k) - E(Costs_k)$$

- Select the strategy with the highest net monetary benefit
- However, Sweden does not have a set willingness-to-pay threshold 😕
  $\Longrightarrow$ look at a range of thresholds

Cost-effectiveness plane assuming systematic biopsies (Karlsson et al, 2021, PLOS ONE)



Acceptability curves (under uncertainty, the proportion cost-effective) assuming systematic biopsies (Karlsson et al, 2021)



Summary of our policy findings

- Using results from a Cochrane Review and assuming PSA testing, MRI was cost-effective compared with systematic biopsies (Hao et al, 2021, Value in Health)
- Assuming systematic biopsies, Stockholm3 test was cost-effective compared with PSA testing at a reflex threshold of 2 ng/mL (Karlsson et al, 2021)
- Assuming MRI and combined systematic/targeted biopsies, Stockholm3 test was cost-effective compared with PSA testing at a reflex threshold of 2 ng/mL (Hao et al, under review)

Discussion

- Next steps:
  - Evaluate MRI in the context of population screening (cf. clinical cohorts; Eklund et al, 2021, NEJM)
  - Evaluate the cost-effectiveness of the different OPT interventions
- Good translational research needs a strong multidisciplinary team – and I would argue that disciplinary isolation leads to poor translations
- Good public health policy should balance the effectiveness of an intervention, including benefits and harms, with the costs

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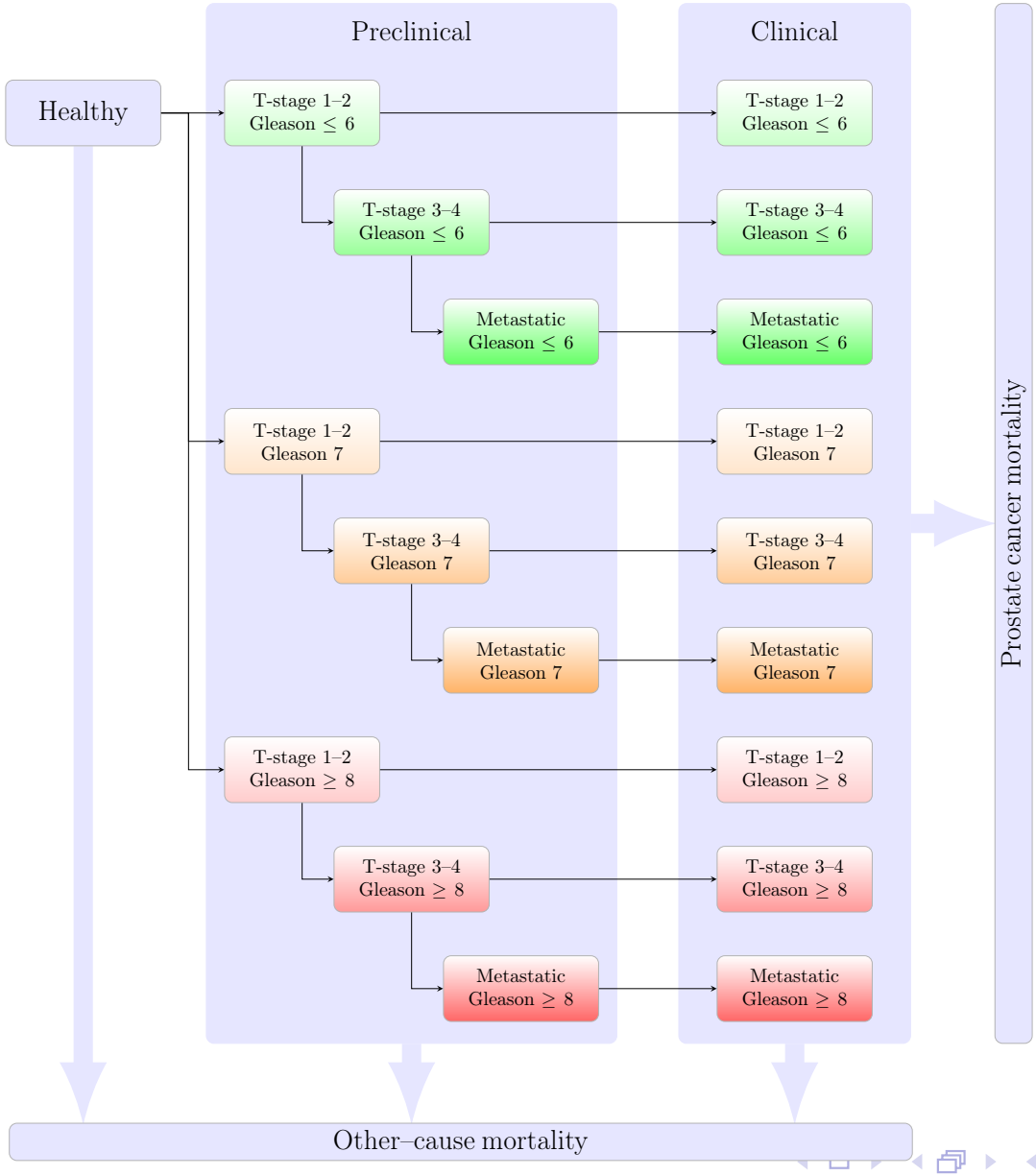
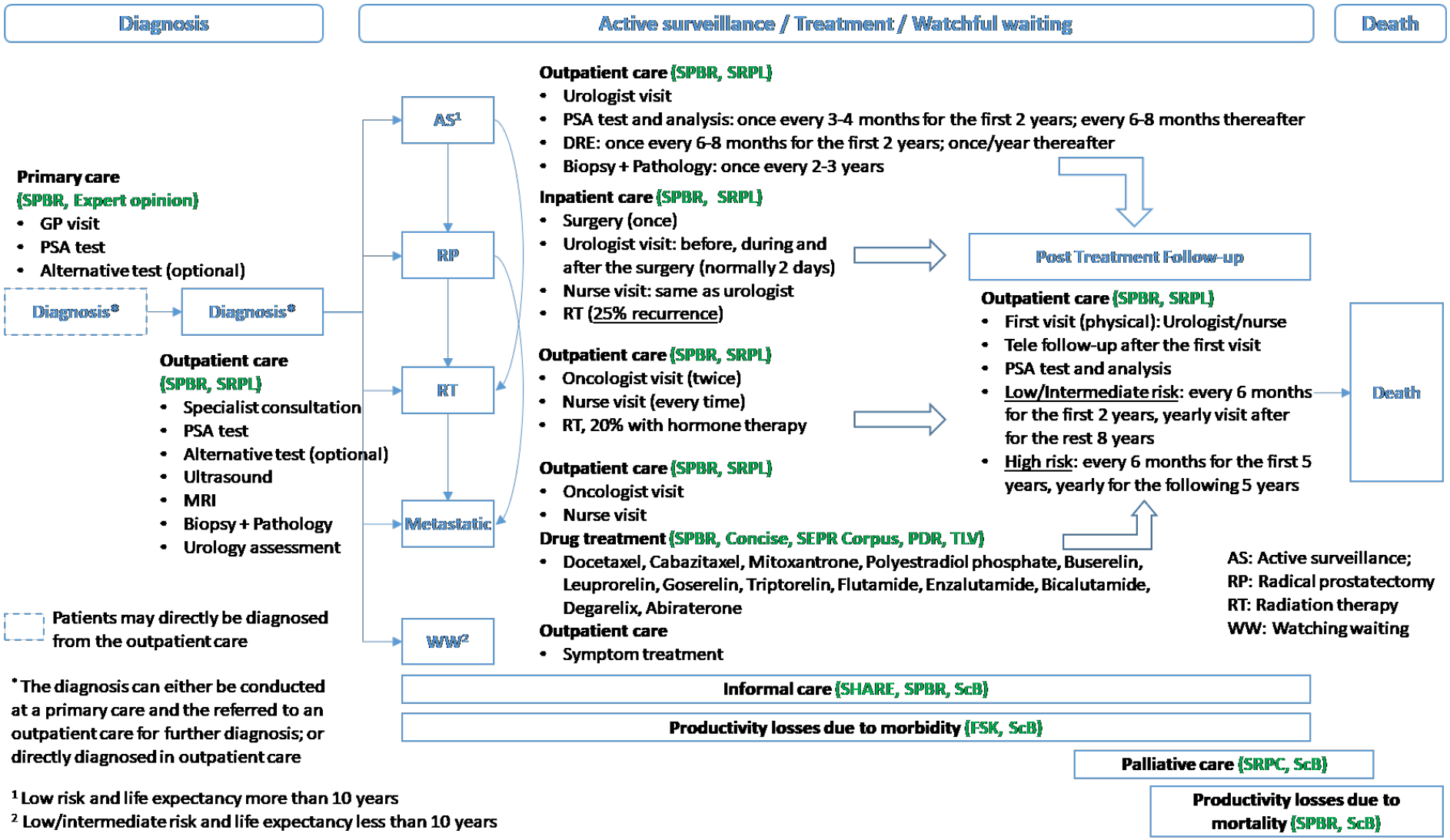
Model schematic (Karlsson et al, 2019, PLOS ONE)



Cost of illness for prostate cancer (Hao et al, 2020, BMC Health Services Research)



Example of simulation output: costs by age