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MIcrosimulation SCreening ANalysis Prostate Cancer Model (MISCAN-Prostate): Model Profile

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Version Table

Version	Date	Notes
1.0.00	2025-09-30	Major update
HI.001.12152009.69754	2009-02-15	Historical release

Other Publications

De Koning HJ, Gulati R, Moss SM, Hugosson J, Andriole GL, Auvinen A, Crawford, Roobol M, Berg C, Nelen V, Kwiatkowski M, Zappa M, Lujan M, Villers A, de Carvalho TM, Feuer EJ, Tsodikov A, Mariotto AB, Heijnsdijk EAM, Etzioni R. The efficacy of PSA screening: impact of key components in the ERSPC and PLCO trials. Cancer. 2018 Mar 15;124(6):1197-1206

Erasmus MC
Readers Guide

Reader's Guide

Core Profile Documentation

These topics will provide an overview of the model without the burden of detail. Each can be read in about 5-10 minutes. Each contains links to more detailed information if required.

Model Purpose
This document describes the primary purpose of the model.

Model Overview
This document describes the primary aims and general purposes of this modeling effort.

Assumption Overview
An overview of the basic assumptions inherent in this model.

Parameter Overview
Describes the basic parameter set used to inform the model, more detailed information is available for each specific parameter.

Component Overview
A description of the basic computational building blocks (components) of the model.

Output Overview
Definitions and methodologies for the basic model outputs.

Results Overview
A guide to the results obtained from the model.

KeyReferences
A list of references used in the development of the model.

Model Purpose

Summary

The MISCAN (MIcroSimulation of CANcer) prostate micro-simulation model is a model based on progression in disease stages and includes prostate cancer natural history, screening, diagnosis, treatment and disease-specific and other-cause death. The model has been used to study epidemiological trends, randomized screening and treatment trials, racial disparities, and alternative implementations of screening and treatment interventions designed to improve long-term harm-benefit tradeoffs in various populations.

Purpose

The MISCAN model was originally developed to quantify the role of PSA screening in prostate cancer incidence and mortality. For this purpose, the model first had been calibrated to the Rotterdam section of the ERSPC trial [1] and later to the entire ERSPC trial [2]. Using the MISCAN model, based on the results of ERSPC Rotterdam, we tried to understand the trends in the US and how they differ from European or Dutch conditions [3]. Also, the models are used to estimate unobservable processes and variables (natural history of the disease, the amount of overdiagnosis and lead time) in the ERSPC trial as well as the US population [1,4,5,6,7,8].

In the first years after the publications of the results of the trials, we have studied the contributions of screening and treatment to a decline in mortality [9-11]. Also, the models have been used to explain the results of the PLCO and ERSPC trials [1,12,13,14].

The impact of active surveillance and different biopsy schedules during active surveillance on overtreatment and mortality have been studied using an extension of the model allowing for following disease progression after diagnosis [15-19].

Finally, the models are used to determine optimal screening ages and test intervals and to calculate QALYs and cost-effectiveness of various screening policies, compared with a situation without screening to optimise strategies to different settings [20-26]. The effects of screening and/or optimal strategies have been determined for populations varying by race [27,28], comorbidity [29], biomarkers [30] and MRI [31,32].

We have demonstrated that MISCAN can be helpful in analyzing and explaining results of cancer screening trials, predicting the (cost-) effectiveness of different screening policies and predicting the potential of present and new interventions on future national trends.

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Model Overview

Summary

This document provides an overview of the MISCAN-prostate model, by describing the model in general terms.

Background

The MISCAN prostate model is one of the MISCAN models developed for evaluating cancer screening. Other models are the colorectal, breast, lung, cervix and esophageal models, also used in CISNET. The models share the MISCAN core code, which is a common set of processes to generate a population, natural history of disease and screening. The MISCAN prostate cancer model has been used to model trends of prostate cancer incidence and mortality in the ERSPC-trial Rotterdam, and in the ERSPC-trial Sweden, the Dutch population and in the US population. With these models it is possible to compare trends of prostate cancer with and without treatment and screening. The base model of MISCAN prostate has been extended to allow modelling active surveillance and to allow for screening protocols based on previous PSA results.

Model Description

MISCAN model is a micro-simulation model. Using the model inputs, independent life histories are generated including a possible cancer history, the effects of treatment and the effects of early detection by screening. The MISCAN-prostate model contains four primary components:

1. Demography component
2. Natural History component
3. Treatment component
4. Screening component.

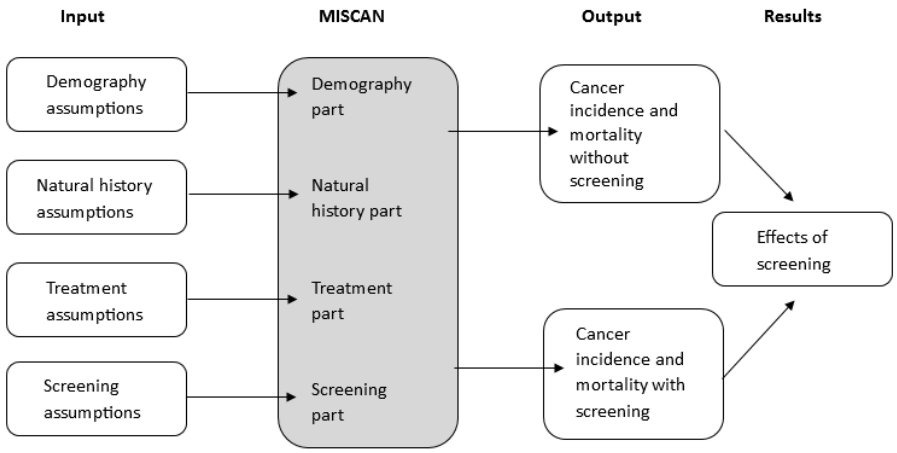

Figure 1. The components in the MISCAN prostate model.

First the demography component simulates a population of individual life histories, according to the demography parameters. Each individual in the population consists of a date of birth and age of death. The parameters of this part (birth tables and life tables) can be adjusted to the population that is being modeled, for example the Netherlands [1], the US [2], The Bahamas [3], or a trial population [4].

Subsequently the natural history component simulates prostate cancer histories for each individual life history separately. Some individuals will have no prostate cancer in their lifetime and others will have prostate cancer

in their lifetime. Once the individual has prostate cancer the cancer can progress to different preclinical states. In the preclinical phase the tumor is asymptomatic, but can be detected by screening. In this definition, the preclinical phase does not only depend on biological processes, but also on the state of medical technology. Eighteen preclinical detectable states are defined by combinations of clinical T-stage (T1, T2 and T3), Gleason grade (6 or smaller, 7, and 8 or larger) and metastatic stage (local-regional and distant). From each preclinical detectable state the cancer can progress to the clinical disease state, which implies that cancer is diagnosed because of symptoms. The parameters (hazard of onset by age, transition probabilities and dwell times) are calibrated to various studies, for example the ERSPC [4].

In the third part the treatment component simulates the life history after clinical diagnosis. Detection with cancer is followed by treatment and possibly prostate cancer death. Different treatments have their treatment-specific survival of prostate cancer death. The distribution of treatment can be adjusted to treatment by age and grade in the modelled population, for example the ERSPC trial [4].

The screening component super-imposes screening on the life histories in the absence of screening. Screening tests applied to a person in a preclinical disease state may result in detection and alter the life history of this individual. Screen detection may alter the cause of events since part of the screen-detected men is cured from cancer and for the other part the life history course will be the same as without screening. The frequency of screening, screening ages, compliance with biopsy and combined sensitivity for PSA and biopsy can be adjusted and/or calibrated for different populations, for example the ERSPC trial [4].

To explicitly model active surveillance (AS), we have developed an extension of the MISCAN model. In the original model, disease progression stops at the moment of clinical or screen-detection and based on age, stage and treatment a men gets a survival time. In the AS model, the progression of disease still continues after diagnosis. Therefore, it is possible to determine the moment of progression of disease from for example Gleason 6 to Gleason7. By modelling biopsies during the AS period, the detection of progression can be modeled and therefore the effect of AS or immediate treatment on overtreatment and prostate cancer mortality [5-9].

Another version of the MISCAN model includes a sub-model for PSA growth. In this model the natural history is still modelled by progression between disease stages, and a PSA growth function is added. A man's PSA level is dependent on age and age of onset. Men having PSA level above a given threshold receive a biopsy and depending on the sensitivity of the biopsy the cancer can be detected. This model has been used in several studies and is currently being updated [3,10,11].

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Assumption Overview

Summary

This documents describes the assumptions in the demography, natural history, screening and treatment part of the MISCAN-prostate model.

Background

The MISCAN prostate cancer model can be used to simulate prostate cancer screening and treatment policies in a dynamic population, based on assumptions on demography, natural history of prostate cancer, treatment and screening. Most of the assumptions relate to the unobservable part in the screening and treatment of prostate cancer: the natural history of the disease and the effect of screening on survival.

Assumption Listing

Demography

- The (country specific) life table is the same for all men in the same birth cohort
- Death from prostate cancer and death from other causes are independent
- The life time prostate cancer risk is the same for all men in a the same birth cohort

Natural history

- Tumor onset:
    - Tumors are assumed to initiate with the same age specific initiation rate for all men.
- Progression of disease:
    - There are eighteen preclinical detectable states which are derived from combinations of clinical T-stage (T1, T2 and T3), Gleason grade (Gleason 6 or less, 7 and 8 or more) and metastatic state (M0 and M1). At onset, the tumour starts in the preclinical stage Gleason 6, T1 and M0.
    - Progression is defined by a matrix of transition probabilities between states, and dwelling time distributions for the time spent in each state. The dwelling times are determined by Weibull distributions.
    - A correlation between duration in subsequent states is assumed, to model fast and slow growing tumors.
    - In each preclinical state there is a probability to transit to the next state (in Gleason or T stage), or to clinical detection.
    - During the period in a state, there is a hazard to progression from a localized/regional state to a metastatic state. This hazard is higher for more progressed states.
    - In any state in the preclinical phase the cancer can be detected by screening.
- Clinical detection:
    - From each preclinical detectable state the cancer can progress to the clinical disease state, which implies that cancer is diagnosed because of symptoms. The progression to the clinical state is defined by the matrix of transition probabilities between states, and dwelling time distributions determined by Weibull distributions, with higher probabilities for more progressed cancers.
    - To account for a higher incidence and a more favorable stage distribution in the control arm of the trials compared to incidence in the US and Dutch population before the trials, it is assumed that in the trial population prostate cancer was clinically diagnosed earlier than in the baseline situation in 1991. Specifically, it is assumed that the hazard of being clinically diagnosed is larger. This difference can for instance be attributed to changes in clinical practice leading to

earlier diagnosis, for example the use of PSA testing for symptomatic disease in a clinical setting.

Treatment

After prostate cancer diagnosis the treatments radical prostatectomy, radiation therapy and active surveillance can be assigned.

Treatment dissemination:

ERSPC model: treatment is modeled as a multinomial logit model with covariates age, T-stage and Gleason score at diagnosis. The categories of the multinomial model are radical prostatectomy, radiation therapy and active surveillance. The parameter estimates are based on data of the Rotterdam section of the ERSPC trial from the year 2000.
US model: treatment is modeled as a multinomial logit model with covariates age, year and grade at diagnosis. The categories of the multinomial model are radical prostatectomy, radiation therapy and active surveillance. The parameter estimates are based on SEER data.

Survival after treatment:

Baseline survival:
The baseline survival has been estimated from SEER (Surveillance, Epidemiology and End Results) data in the pre-PSA era, specifically of cases diagnosed between 1983 and 1986. The survival curves are modeled using Poisson regression with grade, stage, age and treatment type as explanatory variables. To not over-project observed prostate cancer mortality we included a baseline survival hazard ratio to improve the baseline survival, reasoning there have been improvements in disease management since the period 1983-1986 beyond screening or primary treatment.

Treatment effect:
This baseline survival is improved for localized cases who received radical prostatectomy, or radiation therapy using a hazard ratio, obtained from treatment trials. For distant prostate cancer it is assumed that treatment has no effect on the survival, implying that irrespective of the treatment type all men diagnosed with prostate cancer in the distant stage have a survival generated from the corresponding baseline survival curve.

Effect of screening on mortality:
The mortality benefit of PSA screening is modeled as a cure probability that depends on the lead time (years by which detection of the cancer is advanced by screening compared to the clinical situation) and is implemented only for screen-detected, non-metastatic, and non-overdiagnosed cases as cure probability = 1 – exp (-cure parameter x lead time), Figure 1 [1]. Thus the probability of cure increases with lead time, with diminishing incremental benefit for longer lead times. Cured men are assigned to die at their independently generated date of other-cause death. Men who are not cured die at the same time they would have died if they had not been screened.

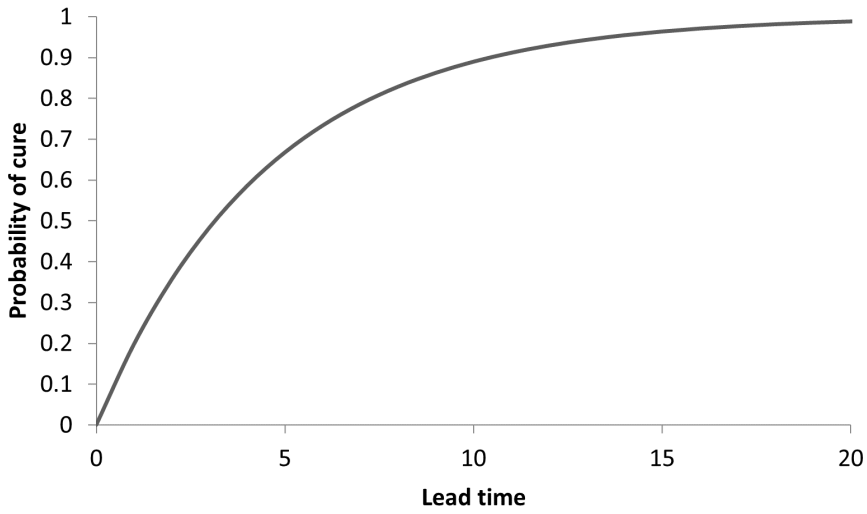

Figure 1. The lead time-dependent cure rate calibrated to the ERSPC trial.

Screening

- Attendance to screening:
    - In the model, men can only be screened when they are still alive at the moment of the screen and when they have not already been diagnosed with prostate cancer.
    - Per cohort, a probability to attend a test at a certain age is assigned.
    - Also per cohort, a probability to attend a test if the previous test has been attended, and if not attended is assigned.
- Sensitivity of the test:
  In the base model, PSA screening and subsequent biopsy are modeled as one single test. The test has a T-stage-dependent sensitivity, calibrated to for example the ERSPC trial. We do not model digital rectal exam (DRE) explicitly.

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Parameter Overview

Summary

Provides a complete overview of the parameters used in the MISCAN-prostate model.

Background

The MISCAN-Prostate model consists of four basic components: The demography component, the natural history component, the treatment component and the screening component. Each component has its own set of parameters.

Parameter Listing Overview

Demography Parameters

- Number of birth cohorts
- Proportion of the population in each birth cohort
- For each birth cohort probability to be born by year
- For each birth cohort probability to die by age

Natural history Parameters

- Hazards for the age specific distribution of onset of the first screen detectable state
- For each birth cohort the life time prostate cancer risk
- The distribution of the duration in each preclinical state
- The transition probability in each preclinical state
- Hazard of metastatic state in each preclinical state
- Correlation between duration in subsequent states
- Baseline prostate cancer survival for survival after clinical diagnosis by age, year, grade and stage of disease at diagnosis and race
- Improvement in baseline prostate cancer survival over time

Screening Test Parameters

- Dissemination of PSA screening by age and year
- Test-sensitivities, including biopsy compliance and biopsy sensitivity, depending on stage, age and period
- Cure rate defining the benefit because of early detection, depending on lead time

Treatment parameters

- Dissemination of treatment by age at diagnosis, year of diagnosis, grade and stage of disease at diagnosis
- Hazard ratios associated with radical prostatectomy, radiation therapy (constant for all individuals)

Parameter estimation

Model parameters for the natural history component and the test-sensitivity are estimated as follows: A model is constructed for a specific situation, such as prostate cancer incidence in the US or both arms of the ERSPC trial Rotterdam. Parameters are then estimated by numerical minimization of the deviance between observed numbers of cases and the corresponding numbers predicted by the model. Deviances are calculated assuming Poisson likelihood for incidence data or a multinomial likelihood for stage distribution data. For the minimization an adapted version of the simplex optimization method of Nelder and Mead is used. Optimization is initiated with small sample sizes and repeated with larger sample sizes (up to 2 million men) when optimization progress is no longer statistically significant.

Component Overview

Overview

As described in the Model overview document, the MISCAN-prostate model contains four primary components: Demography, Natural History, Treatment and Screening.

Demography Component

The demography component simulates a population of individual life histories, according to the demography parameters. Each individual in the population is assigned a date of birth and a date of death. It is possible to define a dynamic population of all ages, which can be adjusted for different countries. Also it is possible to define a cohort of people with the same age or age range.

Natural History Component

The cancer related event history is defined by a sequence of disease states and the ages at which these states are entered. The life histories are generated by a semi-Markov process, defined by a matrix of transition probabilities between states, and dwelling time distributions for the time spent in each state. The disease history is divided in a preclinical phase and a clinical phase. The preclinical phase corresponds to the asymptomatic states. Its parameters have to be estimated from indirect evidence. In the MISCAN prostate cancers model there are eighteen preclinical detectable states which are derived from combinations of clinical T-stage (T1, T2 and T3), Gleason grade (Gleason 6 or less, 7 and 8 or more) and metastatic stage (M0 and M1). The progression through these states is illustrated in Figure 1. From each preclinical detectable state the cancer can progress to the clinical disease state, which implies that cancer is diagnosed because of symptoms.

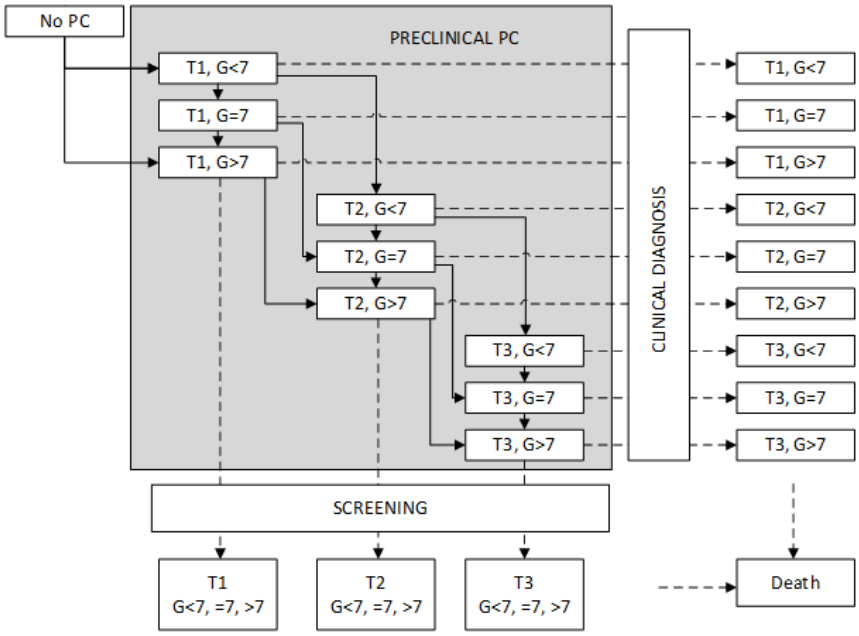

Figure 1. Transitions in the preclinical phase in the MISCAN model. Prostate cancer develops from no prostate cancer via 1 or more screen-detectable preclinical stages to a clinically diagnosed cancer. There is also a distinction between local and metastatic stage, but for simplicity this is not illustrated. Screening is superimposed on the life histories in the absence of screening. Screening may detect cancers earlier in one of the preclinical screen-detectable states.

Screening Component

Screening is super-imposed on the life histories in the absence of screening. Screening tests applied to a person in a preclinical disease state may result in detection and alter his life history. A screening test is defined by its stage-specific sensitivity. A screening policy, is defined by the tests used, attendance rate and screening ages. Screening ages may be selected at regular intervals, or stochastically, allowing the modeling of both regular screening as in trials or screening programs and opportunistic screening. Screen detection may alter the course of events. We assume that the consequence of early detection by screening is that a part of the screen-detected men is cured from cancer and that for the other part detection does not alter the life history.

Treatment Component

The life history after clinical diagnosis is defined by stage-specific survival functions.
Detection with cancer is followed by treatment and a survival of prostate cancer death. Different treatments can be assigned and are followed by a treatment-specific survival of prostate cancer death.

Output Overview

Summary

This document describes the main outputs of the Miscan-prostate model.

Overview

The main outputs of the model are:

- Life histories
- Aggregate outcomes
- Incidence data
- Mortality data

Life histories

Simulated individual life histories reflect preclinical and clinical events and their characteristics over time. A typical model run tracks events with and without assumed screening interventions and includes:

- Age at preclinical onset of prostate cancer
- Age at progression to a next preclinical stage
- Age at prostate cancer diagnosis without screening
- Grade at prostate cancer diagnosis (Gleason score ≤6, 7, ≥8)
- Stage at prostate cancer diagnosis (T1, T2, T3)
- Metastatic stage at prostate cancer diagnosis (M0, M1)
- Primary treatment (radical prostatectomy, radiotherapy, conservative management/active surveillance)
- Age at prostate cancer-specific death
- Age at other-cause death

These simulated life histories are written to output files for each screening and treatment intervention considered. Various summary statistics are then calculated using these data. For example:

- Overdiagnosis: the proportion of individuals with prostate cancer diagnosed by screening who would not have been diagnosed without screening before other-cause death.
- Lead time: the time from diagnosis with screening to diagnosis without screening.
- Sojourn time: the time from preclinical onset to diagnosis without screening.
- Prostate cancer survival: the probability of surviving prostate cancer estimated over time since diagnosis or evaluated at a specific point in time (e.g., 20-year survival).

Aggregate outcomes

Specific event counters are tracked for comparative effectiveness and cost-effectiveness analyses. These include:

- Total PSA tests
- Total biopsies
- Total prostate cancer diagnoses by stage, grade and metastatic state
- Screen diagnoses
- Overdiagnoses
- Total treatments, split by type
- Overtreatments
- Prostate cancer deaths
- Other-cause deaths
- Time spent in asymptomatic state
- Time spent in treatment state
- Time spent in end-of-life state

Event counters are output by age and year to facilitate age-based analyses and discounting of future health outcomes (in addition to discounting future costs).

Incidence data

Simulated prostate cancer diagnosis counts and corresponding population counts from which rates can be calculated are tabulated and output by age and year of diagnosis, tumor stage and grade, and mode of detection (i.e., diagnosis with or without screening).

Mortality data

Simulated prostate cancer and other-cause deaths and corresponding population counts from which rates can be calculated are tabulated and output by age and year of death, tumor stage and grade at diagnosis, and mode of detection (i.e., diagnosis with or without screening).

Results Overview

Summary

This document describes selected results of the MISCAN-prostate model.

Prostate cancer incidence in the US

Figure 1 shows the model generally reproduces the incidence in the US in the period 1975-2009 [1].

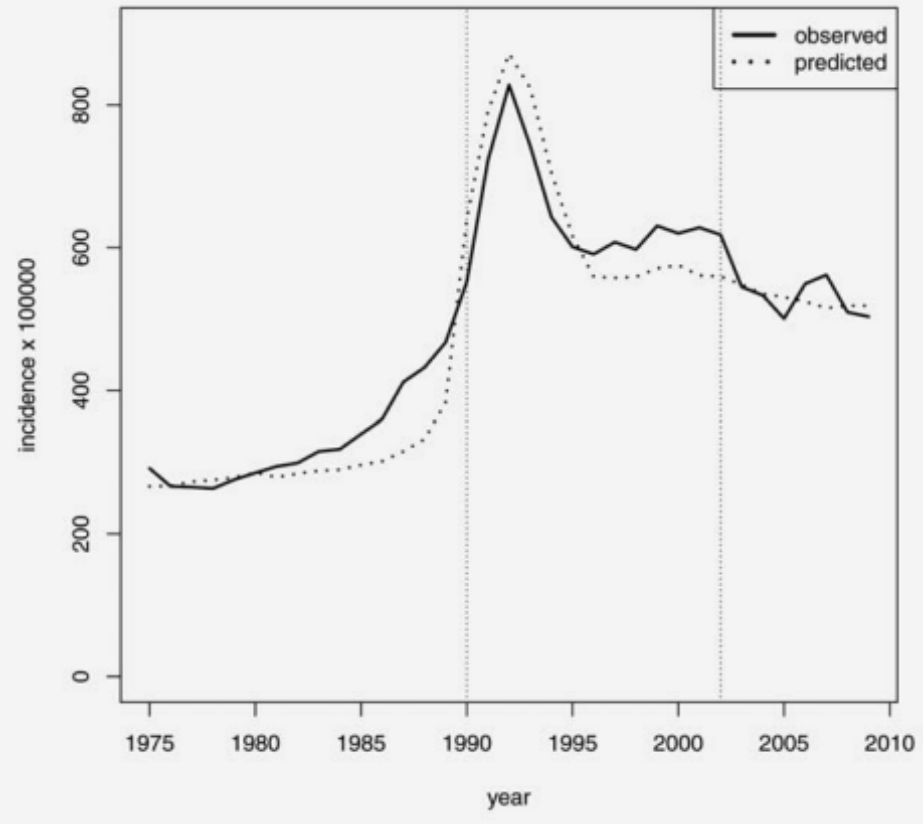

Figure 1. Incidence of prostate cancer in the US population for age-groups 50-85. The data used for calibration is the period between the vertical dots.

Prostate cancer incidence and mortality in the PLCO trial

The calibrated MISCAN model approximately reproduces prostate cancer diagnoses and death in the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial by age, year, stage, grade, and arm [2]. Figure 2 shows observed and projected prostate cancer diagnoses by arm and year after randomization and Figure 3 shows the grade distribution. Figure 4 and 5 show the grade distributions by arm.

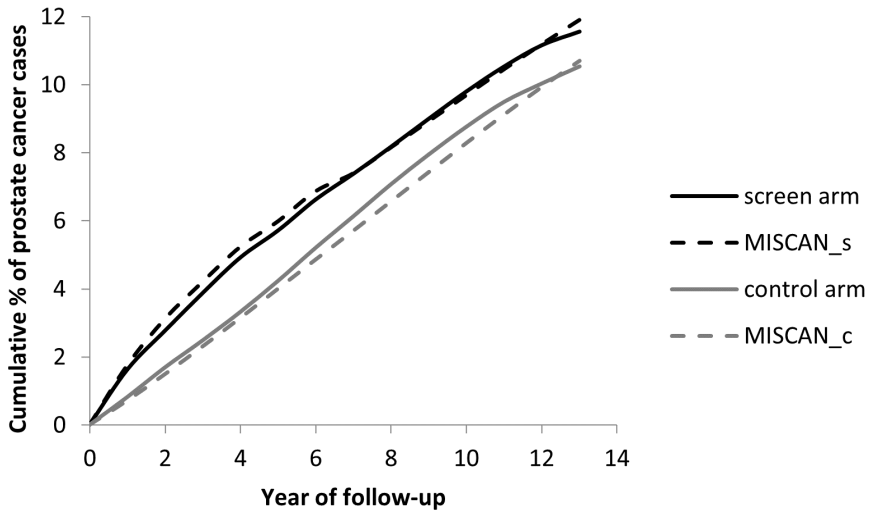

Figure 2. Incidence in the PLCO trial. The solid lines are the observed values in the screen (black) and control (grey) arm. The dashed lines are the MISCAN predictions.

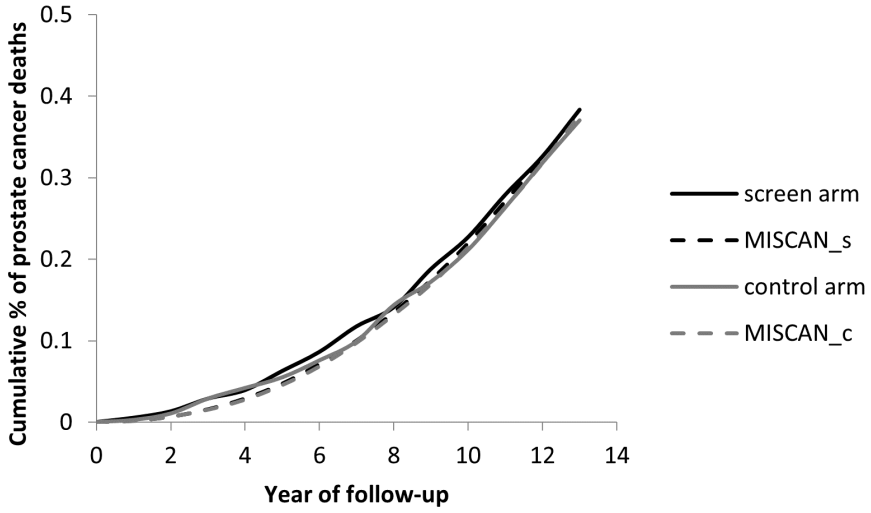

Figure 3. Prostate cancer mortality in the PLCO trial. The solid lines are the observed values in the screen (black) and control (grey) arm. The dashed lines are the MISCAN predictions.

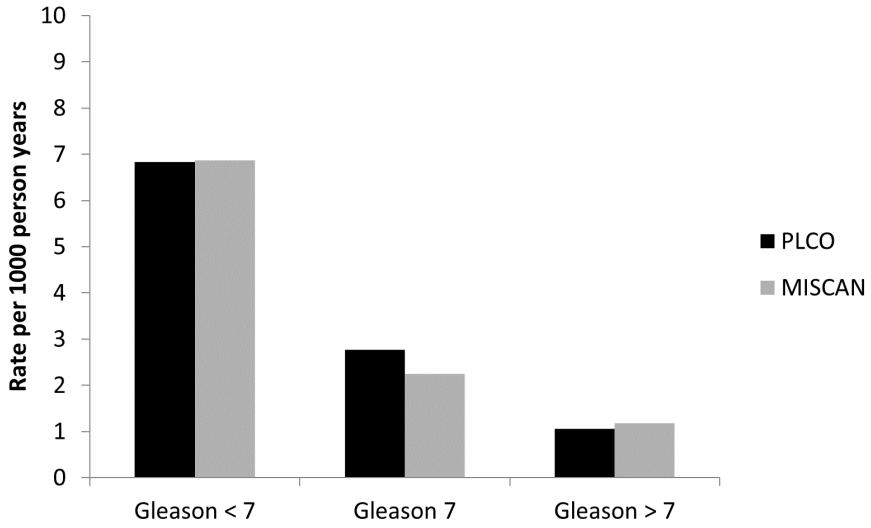

Figure 4. Grade distribution in the screen arm of the PLCO trial.

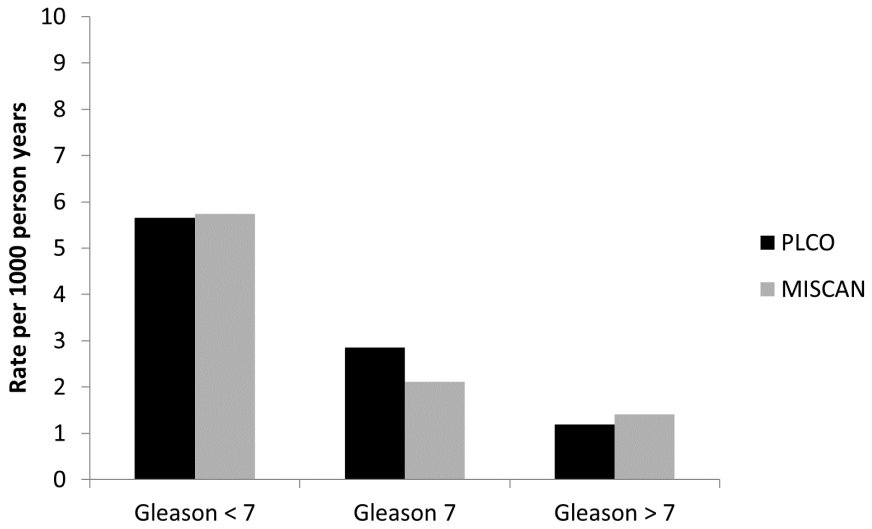

Figure 5. Grade distribution in the control arm of the PLCO trial.

Prostate cancer incidence and mortality in the ERSPC trial

The calibrated MISCAN model approximately reproduces prostate cancer diagnoses and death in the European Randomized Study of Screening for Prostate Cancer (ERSPC) by age, year, stage, grade, and arm [2]. Figure 6 shows observed and projected prostate cancer diagnoses by arm and year after randomization and Figure 7 shows the grade distribution. Figure 8 and 9 show the grade distributions by arm.

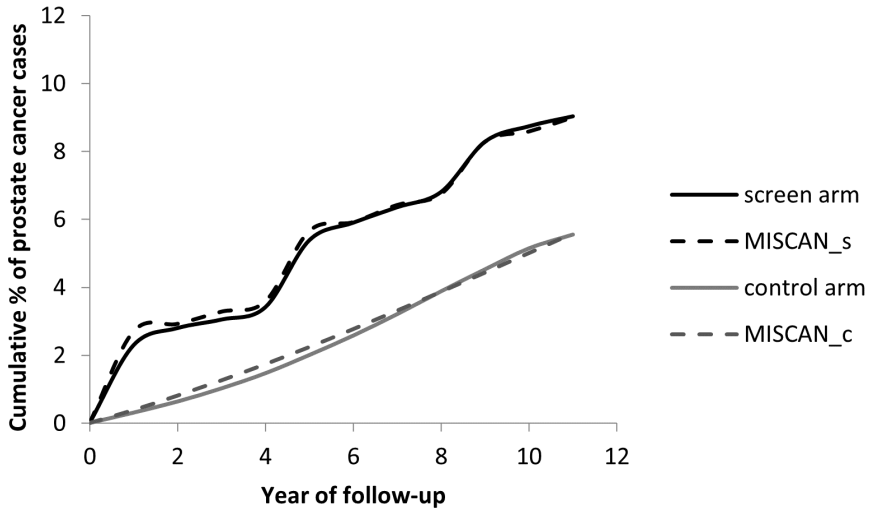

Figure 6. Incidence in the ERSPC trial. The solid lines are the observed values in the screen (black) and control (grey) arm. The dashed lines are the MISCAN predictions.

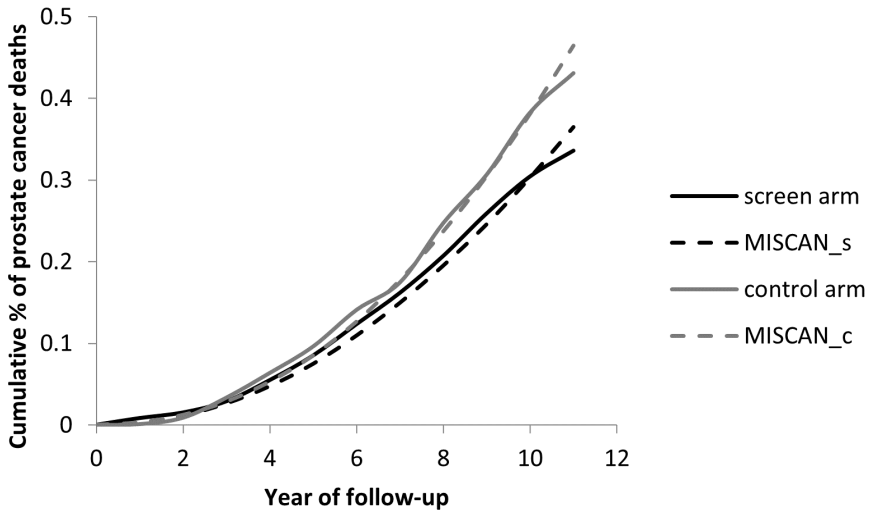

Figure 7. Prostate cancer mortality in the ERSPC trial. The solid lines are the observed values in the screen (black) and control (grey) arm. The dashed lines are the MISCAN predictions.

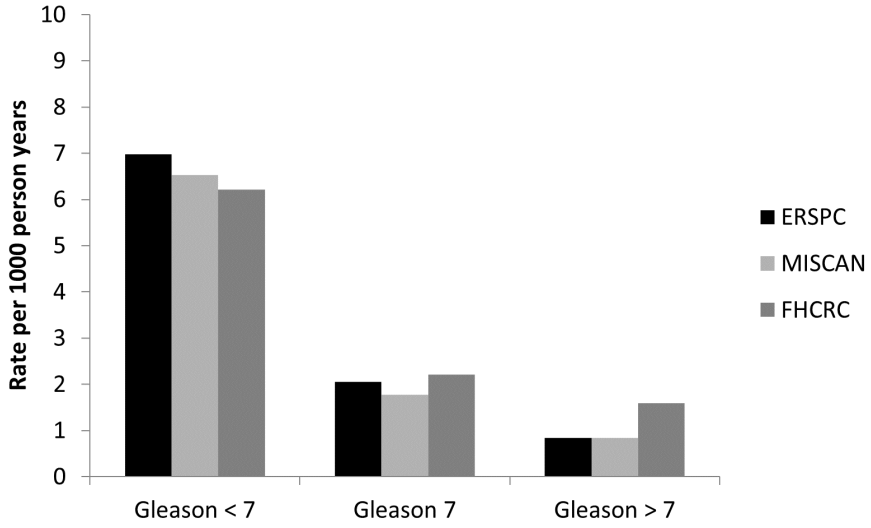

Figure 8. Grade distribution in the screen arm of the ERSPC trial.

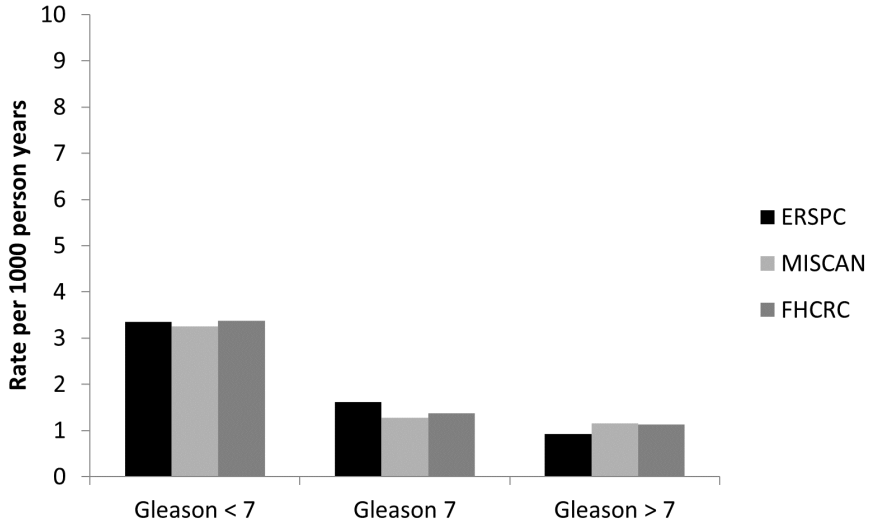

Figure 9. Grade distribution in the control arm of the ERSPC trial.

Cost-effectiveness

Figure 10 shows the cost-effectiveness of different screening protocols, varying by start and end age and screening interval [3].

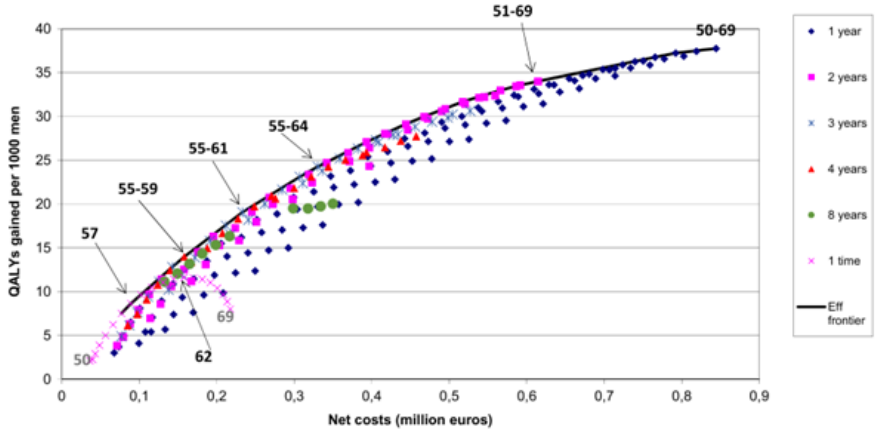

Figure 10. Net costs and QALYs gained per 1000 men. The start and end age of most optimal strategies given 1, 2, 3, 4 and 8 years interval are depicted in the figure. Numbers in the legend indicate the screening intervals used in the mode. Eff frontier = efficient frontier; the strategies leading to the highest QALYs at the lowest costs.

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Validations

Summary

This document describes calibration of the MISCAN-prostate model and selected validations.

Calibration

Over the years, the model has been calibrated to different data sources. In most calibrations, parameters of onset (age-specific hazards), disease progression (transition probabilities and duration in the states), test and/or biopsy sensitivities and PSA growth parameters or subsets of these parameters have been calibrated.
Data sources that are used are:

- SEER prostate cancer incidence by age and year
- Incidence and stage distribution and PSA distributions in the PLCO trial
- Incidence and stage distribution and PSA distributions in the ERSPC trial and in the Rotterdam section of the ERSPC trial
- PSA around age 45 of the Malmo study

Model parameters are estimated by numerical minimization of the deviance between observed numbers of cases and the corresponding numbers predicted by the model. Deviances are calculated assuming Poisson likelihood for incidence data or a multinomial likelihood for stage distribution data. For the minimization an adapted version of the simplex optimization method of Nelder and Mead is used. Optimization is initiated with small sample sizes and repeated with larger sample sizes (up to 2 million men) when optimization progress is no longer statistically significant.
Some results of the calibration are presented in the Results section.

Validation

One of the analyses that demonstrating the validity of the model is the analysis of the ERSPC and PLCO [1]. In this analysis we calibrated the model to the ERSPC data. Starting with reproducing the ERSPC trial, we changed the input one-by-one, ending with a simulation of the PLCO trial. Without changes to the cure parameter, we could reproduce the result of the PLCO trial well within the confidence limits.

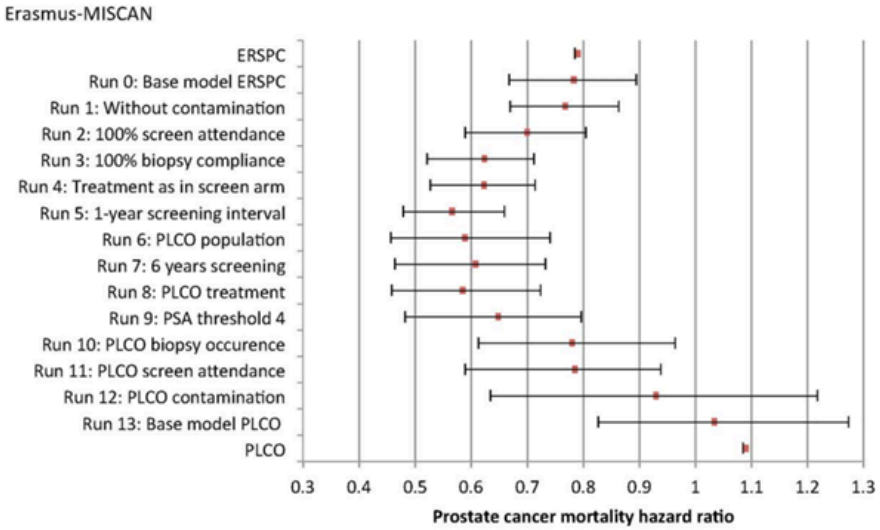

Figure 1. Step-by-step prostate cancer mortality rate ratios and simulation-based uncertainty ranges for the MISCAN model. The changes in the models are cumulative. In run 13, a cure parameter of 0 was used; in all other runs, the European Randomized Study of Screening for Prostate Cancer (ERSPC)-based cure parameter was used. For each run of 0 to 13, 100 simulations of a single ERSPC or Prostate, Lung, Colorectal, and Ovarian (PLCO) trial population were performed to generate sample mortality rate ratios; the line (uncertainty range) and dot represent, respectively, the range and mean of the sample mortality rate ratios observed over the 100 simulations. In runs 0 to 5 a follow-up of 11 years was used, whereas in runs 6 to 13 the follow-up was 13 years. In each step, the listed implementation change was added to the previous step.

Malmo Preventive Project

An external validation of the MISCAN model examined the concordance between model projections and (1) empirical summaries of PSA levels and (2) predicted 25-year risk of prostate cancer diagnosis based on the Malmo Preventive Project stored serum study [2]. Figure 2 shows densities of individual PSA levels observed in the study at ages 44-50 and at age 60 years at venipuncture and corresponding measurements simulated by the MISCAN model. The figure also shows predicted risk of prostate cancer diagnosis from logistic regressions fit to 25-year case status conditional on the (log-transformed) PSA levels.

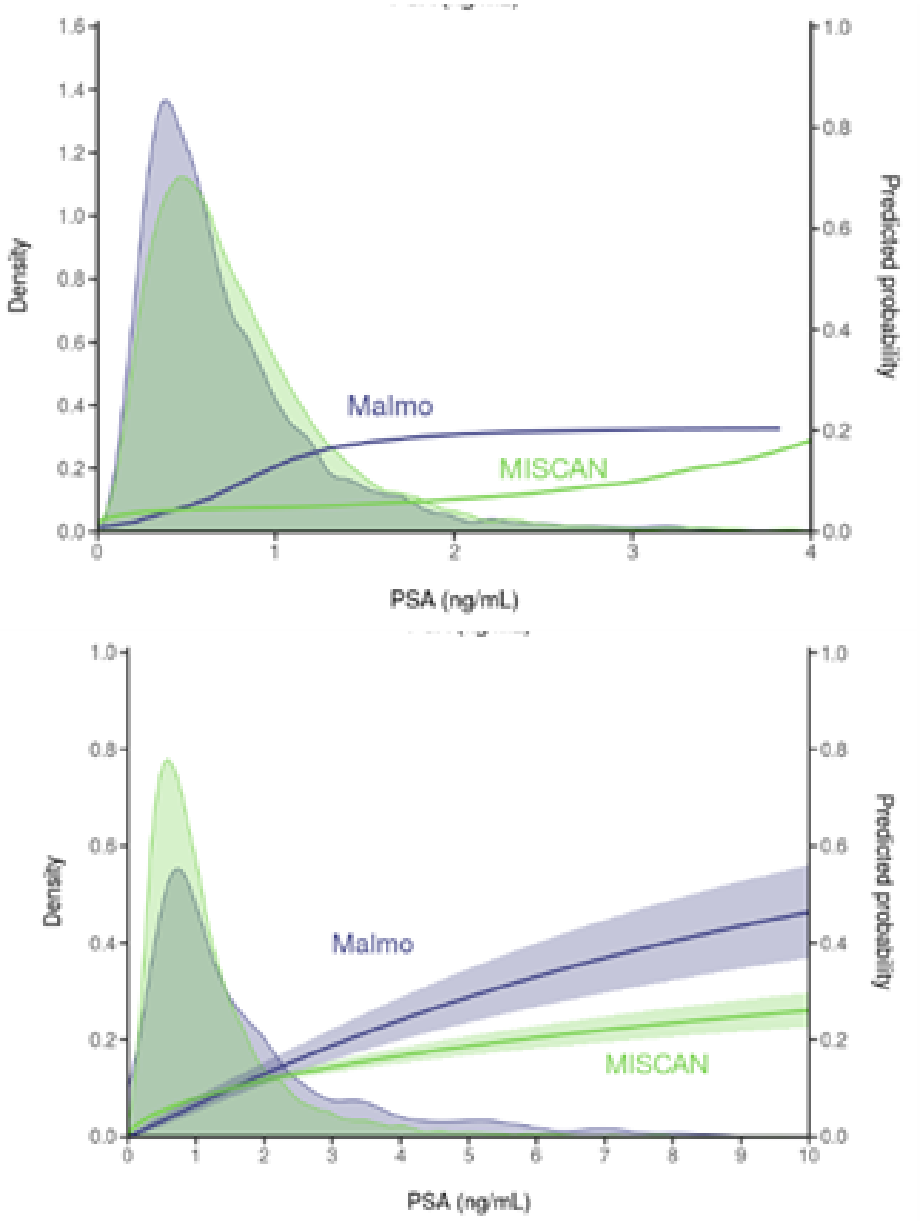

Figure 2. Observed PSA distributions for men ages 44–50 (top) and 60 (bottom) years at venipuncture and predicted 25-year risk of prostate cancer diagnosis based on empirical analysis of Malmo Preventive Project and corresponding projections from the PSAPC model in the absence of screening.

Overall, the model broadly replicates age-specific PSA distributions and empirically estimated risks of diagnosis in the absence of screening in the Malmo Preventive Project.

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