

Appendix

Appendix Table 1a: Complete list of parameters and their distributions for probabilistic sensitivity analyses (continues next page)*

Parameter	Value	Distribution	Parameters
<i>Onset **</i>			
Probability of onset	0.51	Beta	(14160.5, 13605.18)
Hazard onset age 30 and under	-14.34	LogNormal	(2.66, 0.00)
Hazard onset age 30-50	-6.73	LogNormal	(1.91, 0.00)
Hazard onset age 50-70	-3.46	LogNormal	(1.24, 0.00)
Hazard onset age 70 and older	-1.62	LogNormal	(0.48, 0.00)
<i>Transition Matrix (odds of a transition compared to Clinical Diagnosis)</i>			
Odd T1G6 -> T2G6	3.48	LogNormal	(1.23, 0.20)
Odd T1G6 -> T1G7	2.49	LogNormal	(0.89, 0.20)
Odd T1G7 -> T1G8	2.28	LogNormal	(0.80, 0.20)
Odd T1G7 -> T2G7	3.63	LogNormal	(1.27, 0.20)
Odd T1G8 -> T2G8	-7.67	LogNormal	(2.02, 0.20)
Odd T2G6 -> T3G6	1.72	LogNormal	(0.52, 0.20)
Odd T2G6 -> T2G7	0.99	LogNormal	(-0.03, 0.20)
Odd T2G7 -> T3G7	-12.24	LogNormal	(2.49, 0.20)
Odd T2G7 -> T2G8	0.60	LogNormal	(-0.54, 0.20)
Odd T2G8 -> T3G8	-5.25	LogNormal	(1.64, 0.20)
Odd T3G6 -> T3G7	19.92	LogNormal	(2.97, 0.20)
Odd T3G7 -> T3G8	2.47	LogNormal	(0.88, 0.22)
<i>Transition Matrix (durations in each disease stage)</i>			
T1G6	2.67	LogNormal	(0.98, 0.02)
T1G8	13.68	LogNormal	(2.62, 0.02)
T1G7	4.90	LogNormal	(1.59, 0.02)
T2G6	5.19	LogNormal	(1.65, 0.02)
T2G7	11.12	LogNormal	(2.41, 0.02)
T2G8	20.35	LogNormal	(3.01, 0.02)
T3G6	3.27	LogNormal	(1.18, 0.02)
T3G7	10.58	LogNormal	(2.36, 0.02)
T3G8	20.95	LogNormal	(3.04, 0.02)

Appendix Table 1b: Complete list of parameters and their distributions for probabilistic sensitivity analyses (continued)*

<i>Clinical Diagnosis (extra for US population)</i>			
T1 stage	-4.25	LogNormal	(1.44, 0.10)
T2 Stage	-4.15	LogNormal	(1.42, 0.10)
T3 Stage	-3.84	LogNormal	(1.34, 0.11)
Metastasis	5.00	LogNormal	(1.60, 0.10)
Hazard Metastasis #			
T1G6	3.26	LogNormal	(1.18, 0.05)
T1G7	2.63	LogNormal	(0.96, 0.05)
T2G6	1.72	LogNormal	(0.54, 0.05)
T2G7	2.04	LogNormal	(0.71, 0.05)
PSA growth			
PSA growth without onset	0.02	TruncNormal	(0.33, 0.024)
PSA growth after onset	0.33	TruncNormal	(0.02, 0.001)
Screening Parameters #			
Biopsy compliance	0.41	Beta	(991.38, 1426.62)
Attendance	0.9	Beta	(21.6, 2.4)
Sensitivity T1G6	0.85	Beta	(18.42, 3.25)
Treatment and Screening Benefit ***			
Hazard Ratio RT	0.63	LogNormal	(-0.48, 0.17)
Hazard Ratio RP	0.56	LogNormal	(-0.60, 0.19)
Cure parameter	-0.22	Beta	(60.18, 213.38)
Baseline Survival &			
HR baseline survival correction	0.82	LogNormal	(-0.20, 0.03)
Surv.ageDx	0.14	Normal	(0.14, 0.006)
Surv.ageDxG8	-0.16	Normal	(-0.16, 0.002)
Surv	-4.31	Normal	(-4.31, 0.004)
Surv.FU	0.07	Normal	(0.07, 0.001)
Surv.FU2	-0.01	Normal	(-0.01, 0.000)
Surv M1	-2.06	Normal	(-2.06, 0.004)
SurvM1.FU	-0.06	Normal	(-0.06, 0.001)
SurvM1.FU2	-0.01	Normal	(-0.01, 0.000)

* This corresponds to the models used in ^{6,17}.

** The onset function consists of two components. 1) a probability of onset ; 2) the distribution of onset per age is given by a piecewise constant hazard function dependent on age group.

*** The hazard ratios are relative to the baseline survival. Their value and corresponding distributions are based on the literature ^{4,28}. The cure parameter is applied on top of the benefit of treatment.

Some Parameters were excluded.

& HR baseline prostate cancer survival correction (infl.hr) was calibrated to the observed prostate cancer mortality in the control group of the ERSPC trial. The Baseline Survival (for prostate cancer) equation for non-metastatic cases equals,

Prostate Cancer Survival = $\exp(\text{Surv} + \text{Surv.FU}*(t-8) + \text{Surv.FU2}*(t-8)^2) * \text{infl.hr}$,

Where t, is the time since onset. By replacing all “Surv” parameters with the set of “Surv.M1” parameters we obtain the survival for metastatic cases. The parameter Surv.ageDx denotes an age specific factor (at the time of clinical diagnosis) applied to the baseline survival.

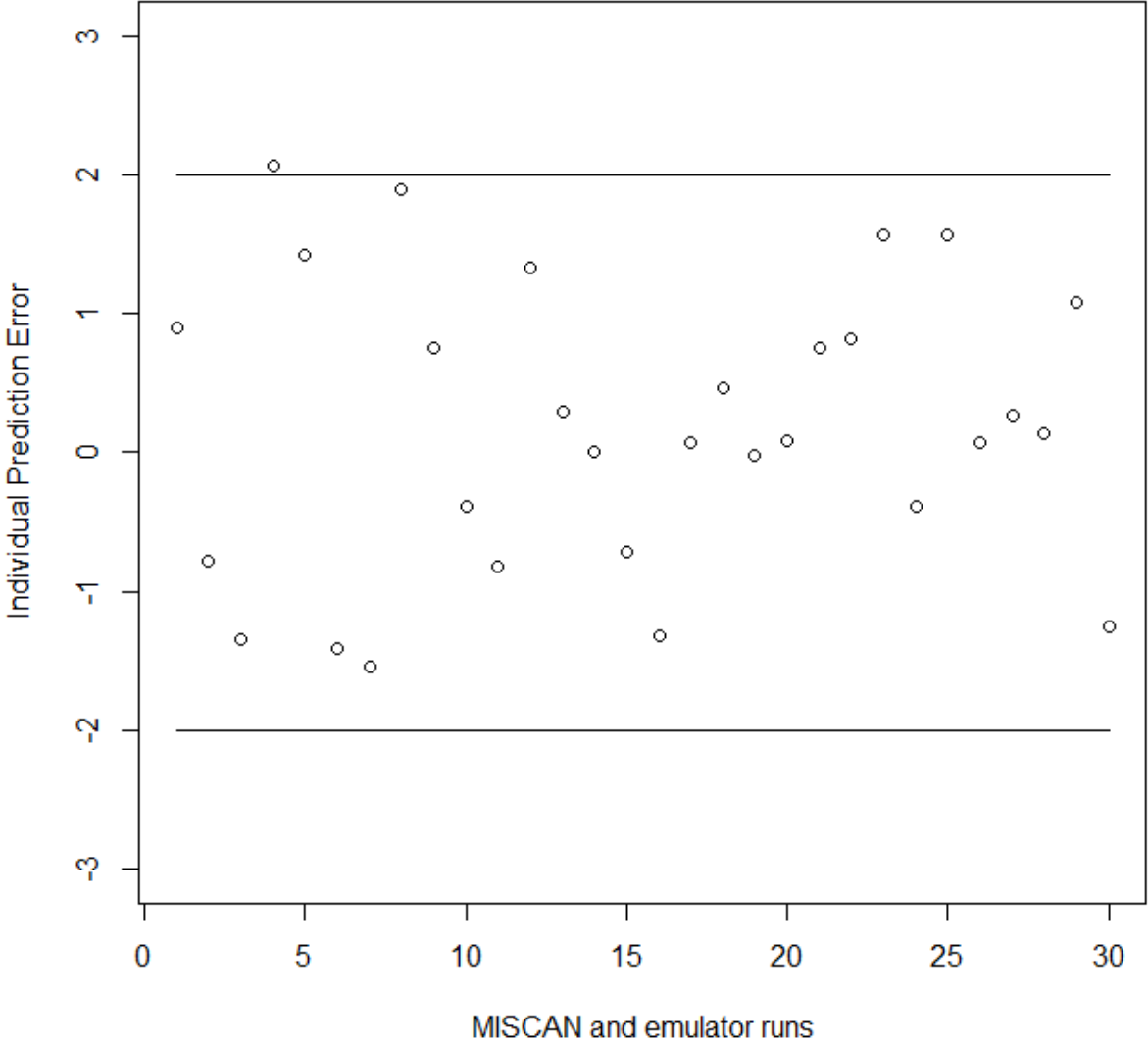
Appendix Table 2: Parameters included in the Gaussian Process emulator.*#

Parameter Name	Coefficient (β)	Correlation Length (ψ)
Probability of onset	0.51	9.45
Hazard onset age 30-50	-6.73	6.16
Hazard onset age 50-70	-3.46	20
Duration T1G6	2.67	2.51
Duration T2G6	5.19	4.73
Clinical Diagnosis T1-Stage	-4.2	2.31
Clinical Diagnosis T2-Stage	-4.15	1.4
Clinical Diagnosis T3-Stage	-3.84	1.74
Biopsy Compliance	0.41	1.48
PSA growth after onset	0.33	0.86

* Contains all parameters included in the emulator. Correlation Length (ψ) parameters were estimated with maximum likelihood estimation. The estimate for the σ^2 parameter equals 4.55 e-05.

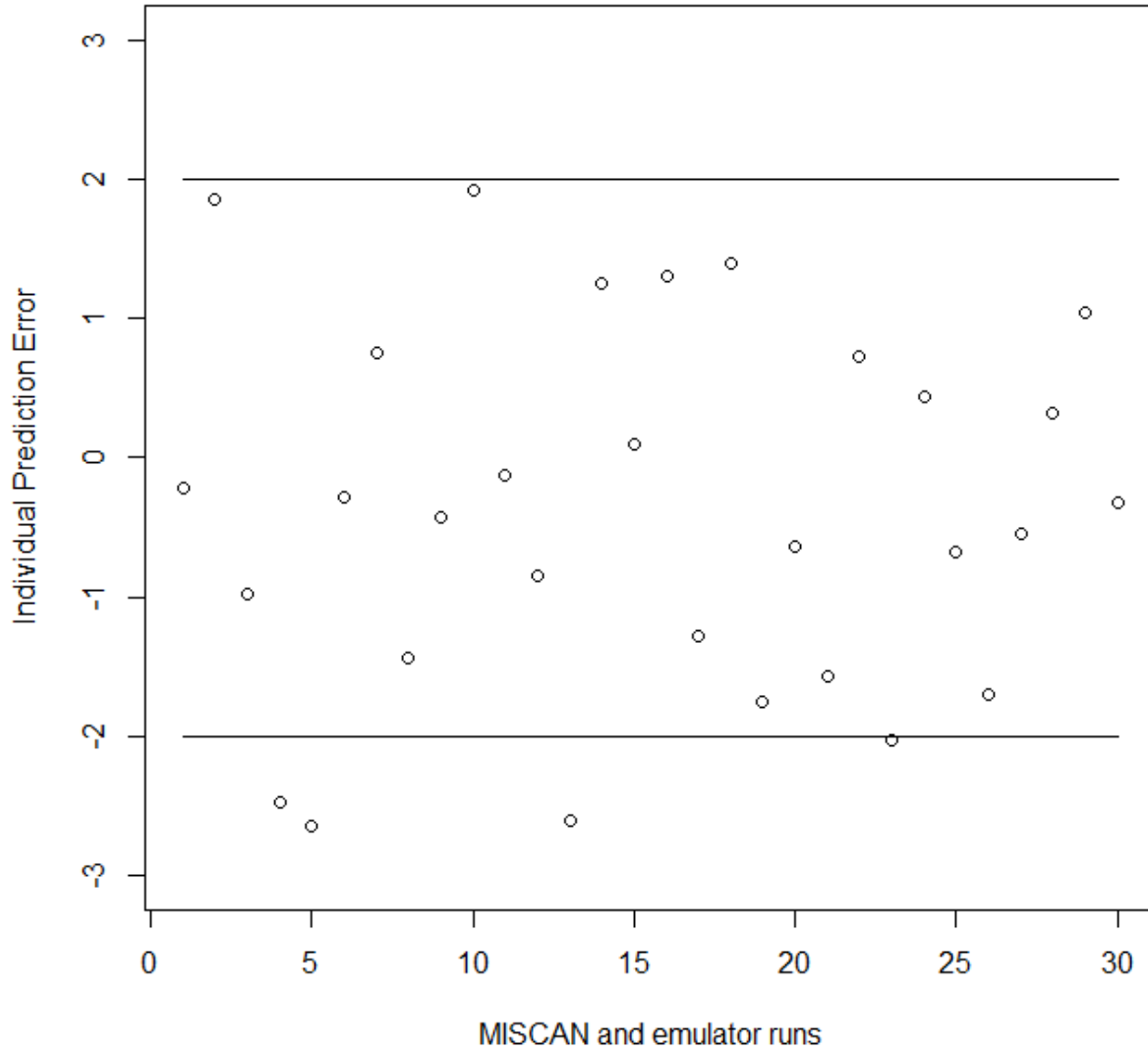
In the 5 parameter run the following parameters were included in the emulator: Probability of onset, Hazard onset age 30-50, Hazard onset age 50-70, Duration T1G6 and PSA growth after onset.

Appendix Figure 1: Standardized Individual Prediction Errors for the overdiagnosis emulator.



* This figure uses data from the first 30 runs (See Appendix Table 3). Standardized Individual Prediction Error is based on ¹⁹. It equals the difference between the emulator prediction and MISCAN output divided by the standard error of the emulator. A value of the individual prediction error higher than 2 indicates a discrepancy between the emulator and the data, since the standardized prediction errors should be normally distributed.

Appendix Figure 2: Standardized Individual Prediction Errors for the prostate cancer mortality emulator.



* This figure uses data from the first 30 runs (See Appendix Table 3). Individual Prediction Error is based on ¹⁹. It equals the difference between the emulator prediction and MISCAN output divided by the standard error of the emulator. A value of the individual prediction error higher than 2 indicates a discrepancy between the emulator and the data, since the standardized prediction errors should be normally distributed.

Appendix Table 3: Mahalanobis distance values for different sensitivity analyses*

Scenario	Mahalanobis Distance
Basecase	9900
Another random number seed	11736
N=50	6509
N=150	11373
5 parameters in emulator	> 1 million
Randomly chosen parameters	2773
True model contains 10 parameters	60
Prostate Cancer Mortality Emulator	1269

* Based on the test given in Bastos and O'Hagan¹⁹. The test was calculated using data from the first 30 runs. Expected value of the Mahalanobis distance statistic is 30. Basecase denotes 100 runs, using 123 as a random number seed and 10 carefully chosen parameters. In *Another random number seed*, seed number 124 is chosen.