

Supplementary Materials

Overdiagnosis and lives saved due to reflex testing men with intermediate prostate-specific antigen levels

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SUPPLEMENTARY TABLES

Supplementary Table 1. Performance of prostate-specific antigen (PSA) and urinary reflex biomarkers for predicting any and high-grade prostate cancer (PCa) in empirical and simulated records of men with PSA between 4.0 and 10.0 ng/mL

Source	Biomarker	Any PCa		High-grade PCa	
		AUC	<i>p</i> value*	AUC	<i>p</i> value*
Empirical	PSA	0.513	ref.	0.564	ref.
	T2:ERG	0.660	<0.001	0.639	0.01
	PCA3	0.716	<0.001	0.710	<0.001
	MiPS	0.739	<0.001	0.733	<0.001
	MiPShg	0.737	<0.001	0.736	<0.001
Model	PSA	0.540	ref.	0.541	ref.
	T2:ERG	0.660	<0.001	0.638	<0.001
	PCA3	0.699	<0.001	0.690	<0.001
	MiPS	0.725	<0.001	0.723	<0.001
	MiPShg	0.723	<0.001	0.728	<0.001

* DeLong's test to compare AUCs. *p* values are two-sided.

T2:ERG=TMPRSS2:ERG gene fusion; PCA3=prostate cancer antigen 3; MiPS=Michigan Prostate Score for any PCa; MiPShg=Michigan Prostate Score for high-grade PCa; AUC=area under the receiver operating characteristic curve

Supplementary Table 2. Predicted immediate and long-term prostate cancer (PCa) outcomes per 1000 men with prostate-specific antigen (PSA) between 4.0 and 10.0 ng/mL at screening age 55 with possible continued biennial screening up to age 69 by biopsy strategy*

Biopsy strategy	Biopsies Done, n	Biopsies, %Δ†	PCa diagnoses, n		Overdiagnoses n	Overdiagnoses %Δ†	Deaths, n		Lives saved, n	Lives saved, %Δ†	Overdiagnoses per life saved
			Low grade	High grade			PCa	Other			
No patients	887	11.3	210	154	60	24.1	43	957	44	20.8	1.3
T2:ERG >5	971	2.9	240	168	74	5.0	34	966	53	5.9	1.4
PCA3 >35	943	5.7	231	165	71	10.0	37	963	50	11.2	1.4
MiPS >30%	979	2.1	243	171	76	2.5	33	967	54	3.7	1.4
MiPShg >10%	989	1.1	244	172	77	1.6	32	968	54	2.9	1.4
IDEAL	947	5.3	248	173	78	0.1	32	968	56	0.0	1.4
IDEALhg	907	9.3	209	173	66	16.2	38	962	50	10.8	1.3
All patients	1000	0.0	248	173	78	0.0	32	968	56	0.0	1.4

* In contrast with Table 3, outcomes in this table are for the initial biopsy decision and any subsequent screening tests/biopsy decisions.

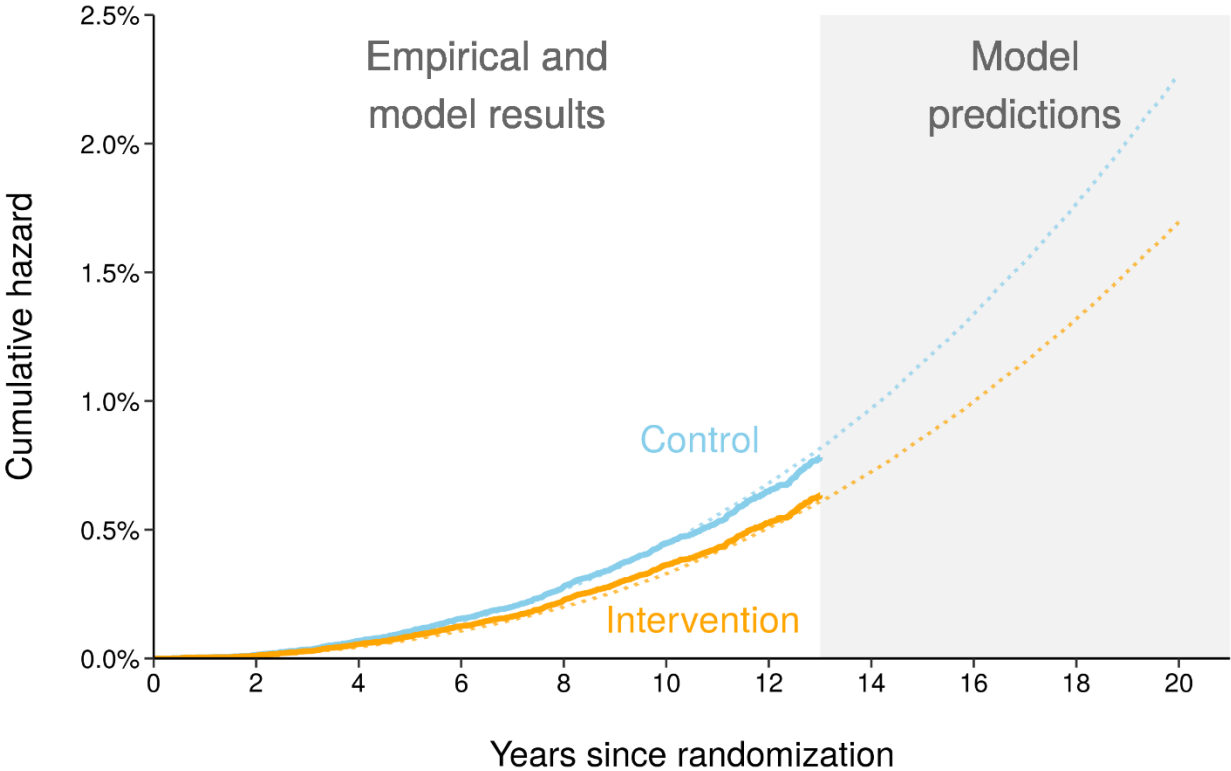
‘Biopsies done’ is the number of men who received at least one biopsy. T2:ERG=TMPRSS2:ERG gene fusion; PCA3=prostate cancer antigen 3;

MiPS=Michigan Prostate Score for any PCa; MiPShg=Michigan Prostate Score for high-grade PCa; IDEAL=ideal biomarker with 100%

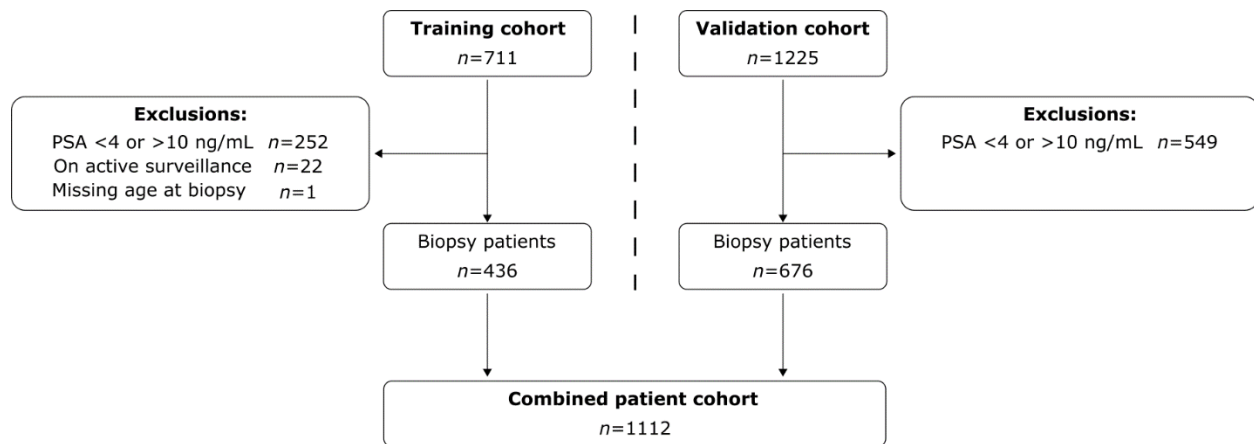
sensitivity/specificity for any PCa; IDEALhg=ideal biomarker with 100% sensitivity/specificity for high-grade PCa

† ‘%Δ’ shows the percent reduction under each biopsy strategy relative to biopsying all patients.

SUPPLEMENTARY FIGURES

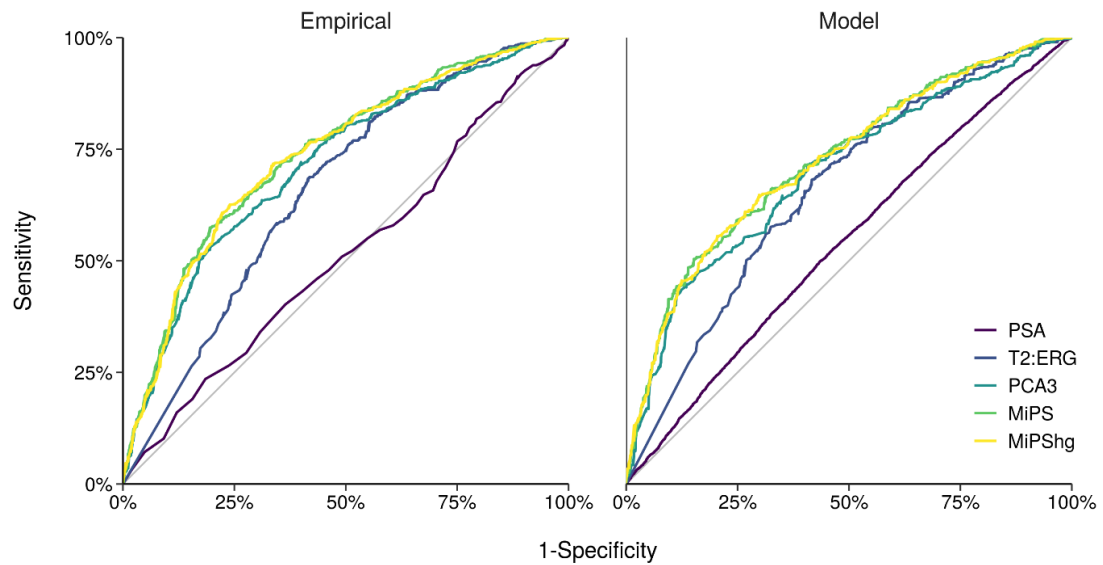


Supplementary Figure 1. 13-year cumulative incidence of prostate cancer death for men ages 55-69 years at randomization in the European Randomized Study of Screening for Prostate Cancer. 20-year predictions from the microsimulation model are also shown.

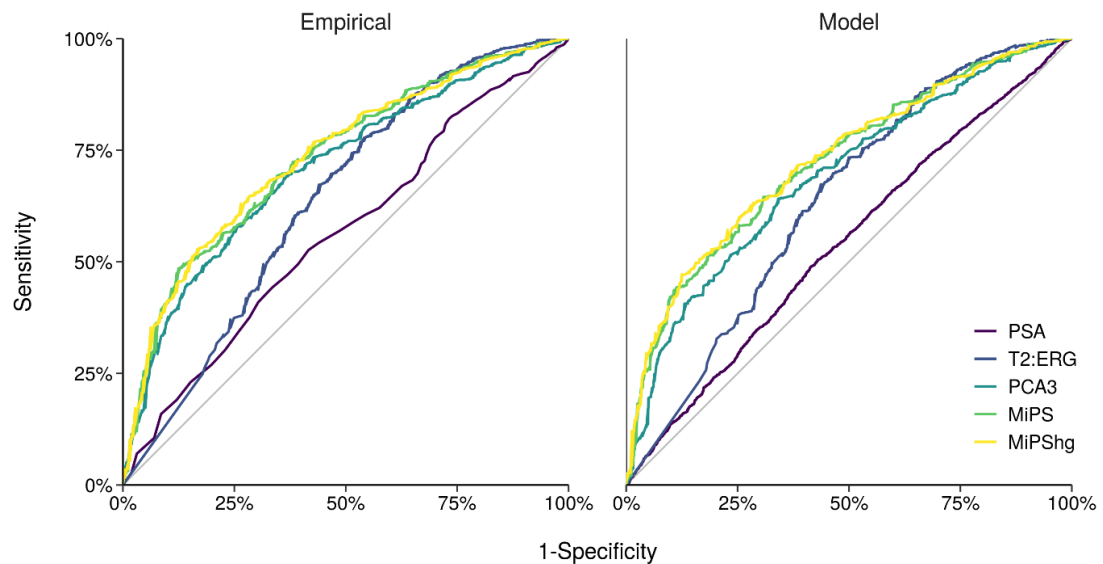


Supplementary Figure 2. Flow diagram of patients with evaluable biopsies. Patients from original training and validation cohorts were combined after indicated exclusions and used to generate urinary reflex biomarker levels in the microsimulation model. PSA=prostate-specific antigen

(A) Any PCa



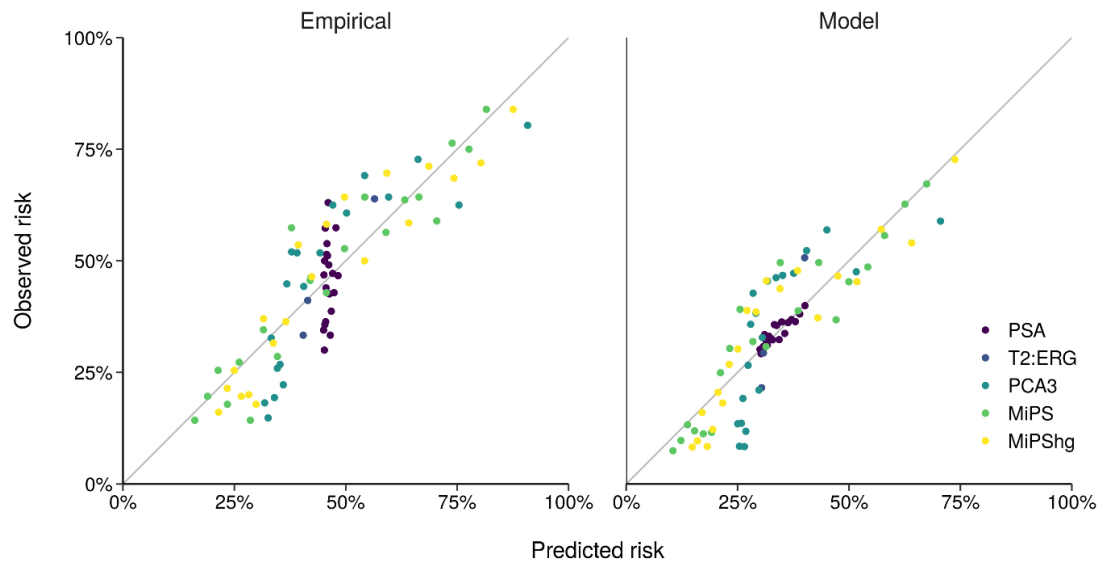
(B) High-grade PCa



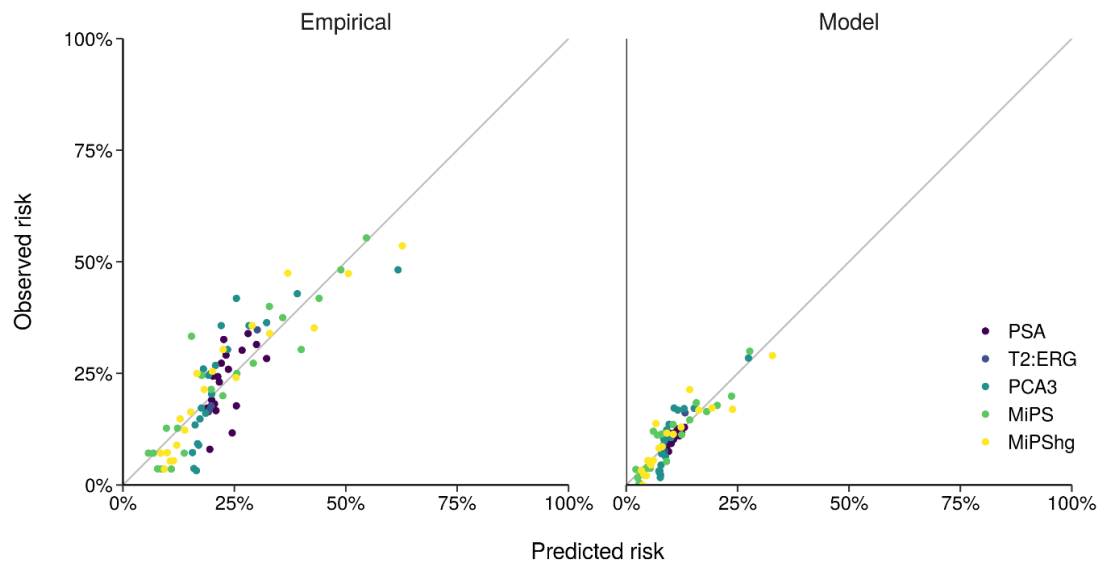
Supplementary Figure 3. Discrimination of empirical and modeled urinary reflex biomarkers in men with prostate-specific antigen (PSA) between 4.0 and 10.0 ng/mL. Receiver operating characteristic curves for detecting any PCa (A) and high-grade PCa (B) are shown for each biomarker.

T2:ERG=TMPRSS2:ERG gene fusion; PCA3=prostate cancer antigen 3; MiPS=Michigan Prostate Score for any PCa; MiPSHg=Michigan Prostate Score for high-grade PCa

(A) Any PCa

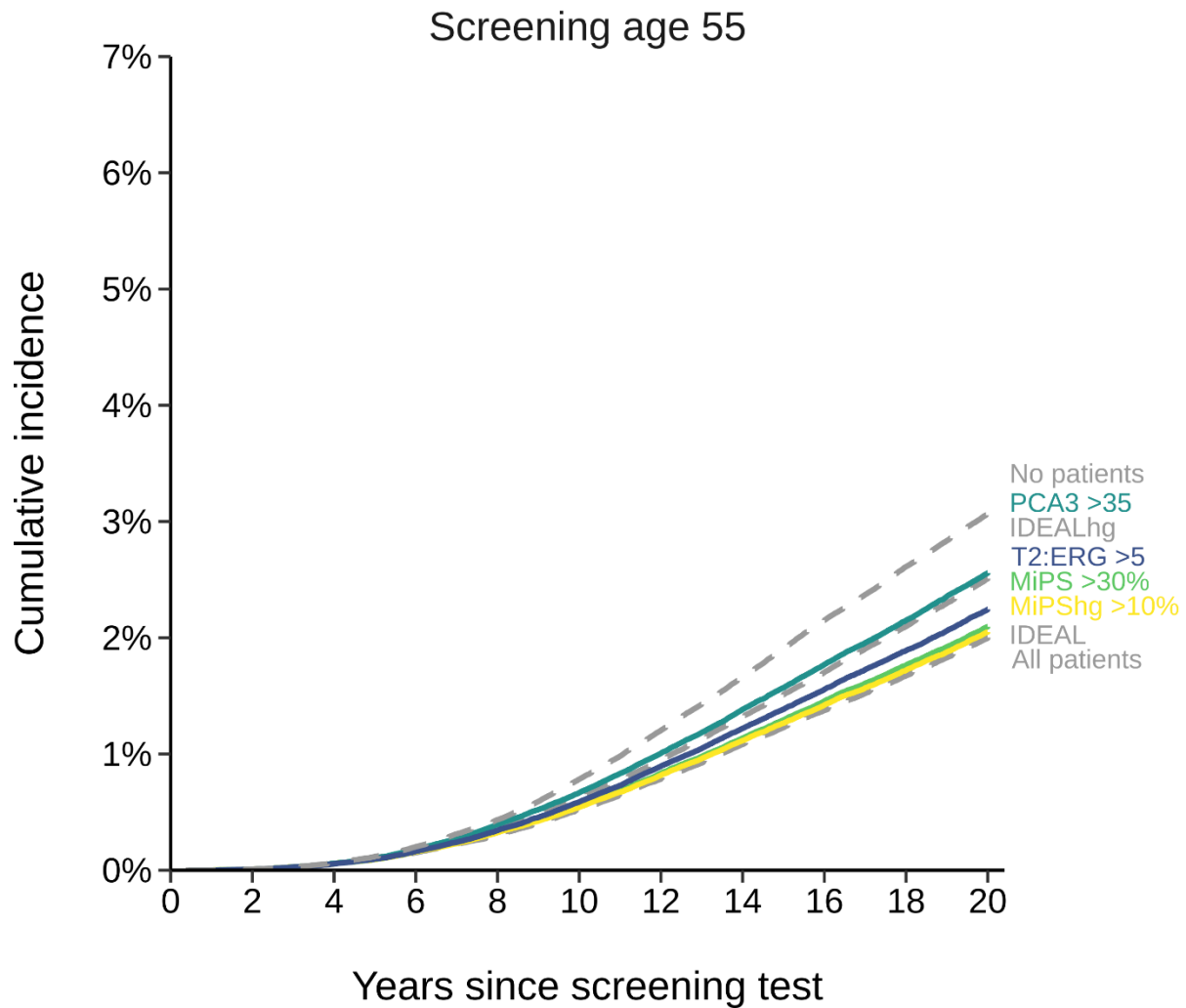


(B) High-grade PCa



Supplementary Figure 4. Calibration of empirical and modeled urinary reflex biomarkers in men with prostate-specific antigen (PSA) between 4.0 and 10.0 ng/mL. Calibration plots for detecting any PCa (A) and high-grade PCa (B) are shown for each biomarker.

T2:ERG=TMPRSS2:ERG gene fusion; PCA3=prostate cancer antigen 3; MiPS=Michigan Prostate Score for any PCa; MiPShg=Michigan Prostate Score for high-grade PCa



Supplementary Figure 5. Predicted 20-year cumulative incidence of prostate cancer (PCa) death for men with prostate-specific antigen (PSA) between 4.0 and 10.0 ng/mL at screening age 55 with possible continued biennial screening up to age 69 by biopsy strategy.

T2:ERG=TMPRSS2:ERG gene fusion; PCA3=prostate cancer antigen 3; MiPS=Michigan Prostate Score for any PCa; MiPShg=Michigan Prostate Score for high-grade PCa; IDEAL=ideal biomarker with 100% sensitivity/specificity for any PCa; IDEALhg=ideal biomarker with 100% sensitivity/specificity for high-grade PCa.