OVERDIAGNOSIS

The Balance of Benefit, Harm, and Cost of PSA Screening

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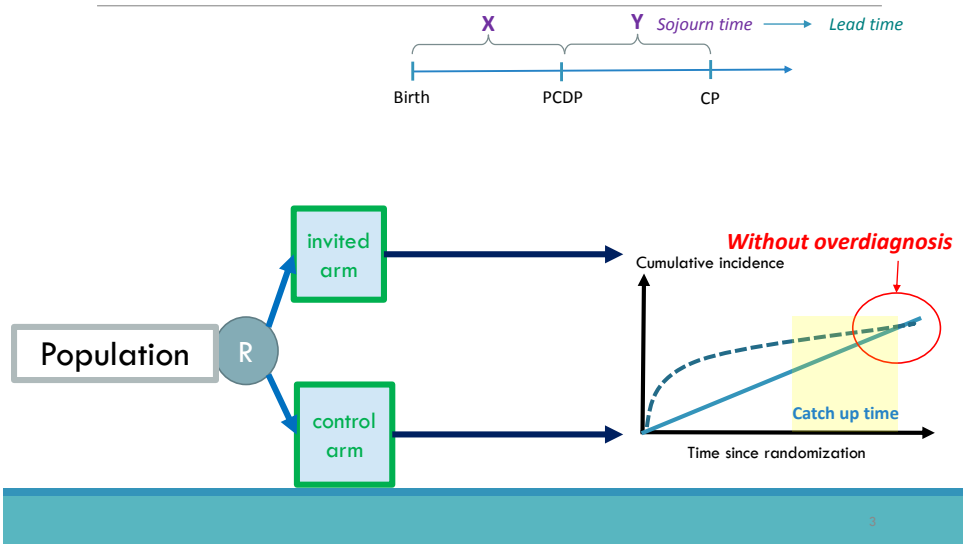
Overdiagnosis Issues in Population-based Cancer Screening

Heterogeneous Definitions of Overdianosis
- Disease status and competing causes of death
- Diagnosis and detection modality

Methodological Flaws in Estimation of Overdiagnosis
- Lead-time and Length bias
- Measurement errors of screening modalities
- Disease natural history

Unobservable Phenomenon
- Design-based Study
- Model-based approach

Natural Disease Progression Related to Lead-time and Overdiagnosis and Evaluation with RCT



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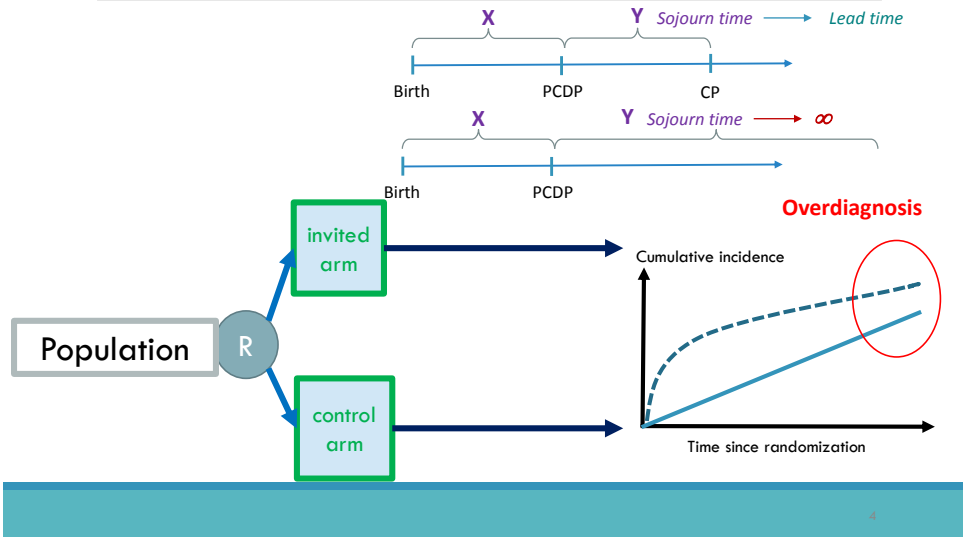

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Prostate cancer

Help or harm

The furious debate over screening for prostate cancer

Mar 8th 2014 | From the print edition

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The Great Prostate Hoax: How Big Medicine Hijacked the PSA Test and Caused a Public Health Disaster. By Richard Ablin and Ronald Piana. *Palgrave MacMillan; 262 pages; $27. Buy from Amazon.com, Amazon.co.uk*

Cost-effectiveness Analysis for PSA Screening

PSA screening
(RCT trial: PLCO, ERSPC)

↑

controversial

→

Benefit
- Reducing prostate cancer (PCa) mortality
- Enhanced QoL

Harms
- False positive, overdiagnosis
- False negative

To perform a **decision analysis** using a **Markov model** to compare the **effectiveness** and **cost** of PSA screening with no screening with the considerations of **harms** and **cost** of screening

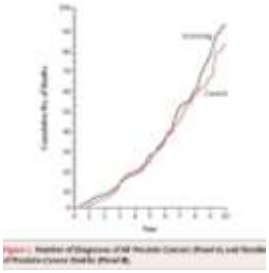
Screening for Prostate Cancer with PSA Test

The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (PLCO)
The European Randomized study of Screening for Prostate Cancer (ERSPC)

The NEW ENGLAND JOURNAL of MEDICINE

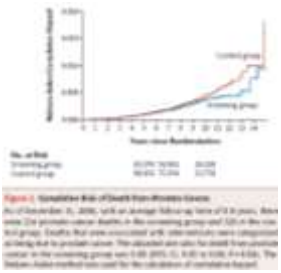
ORIGINAL ARTICLE

2009;360:1310-9.



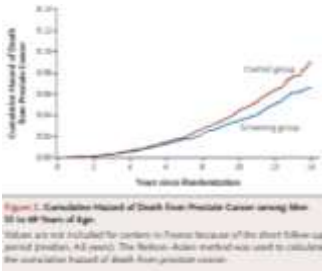
PLCO, 7-yr follow-up
RR=1.13 (0.75-1.70)

2009;360:1320-8.



ERSPC, 8-yr follow-up
RR=0.80 (0.65-0.98)

2012; 366: 981-90



ERSPC , 11-yr follow-up
RR=0.79 (0.68-0.91)

Age-Adjusted Incidence of and Mortality from Prostate Cancer in the United States, 1975–2007

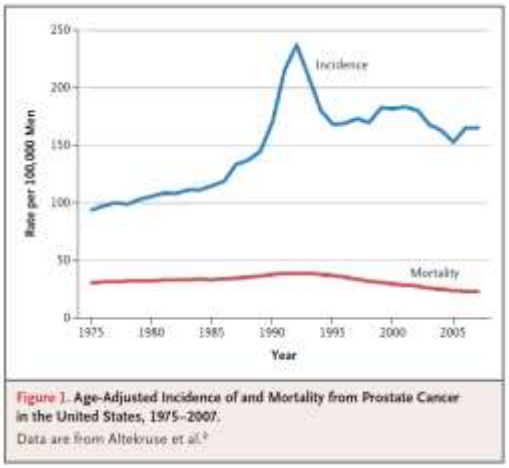


Figure 1. Age-Adjusted Incidence of and Mortality from Prostate Cancer in the United States, 1975–2007.
Data are from Altekruse et al.[1]

CLINICAL PRACTICE

Screening for Prostate Cancer

N Engl J Med 2011;365:2013-9.

Reference: Altekruse SF, Kosary C, Krapcho M, et al. SEER cancer statistics review 1975-2007. Bethesda, MD: National Cancer Institute, 2010.

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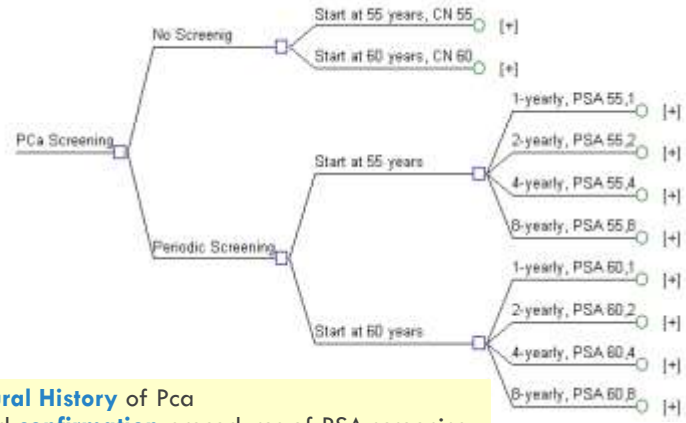
Markov Decision Tree for PSA screening



- ✓ **Disease Natural History** of Pca
- ✓ **Screening** and **confirmation** procedures of PSA screening
- ✓ **Treatment** module of PCa

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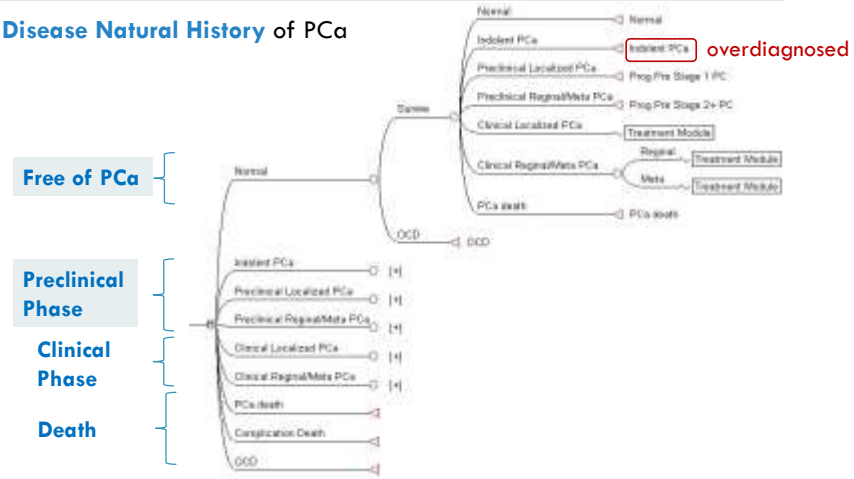
Markov Decision Tree

Disease Natural History of PCa



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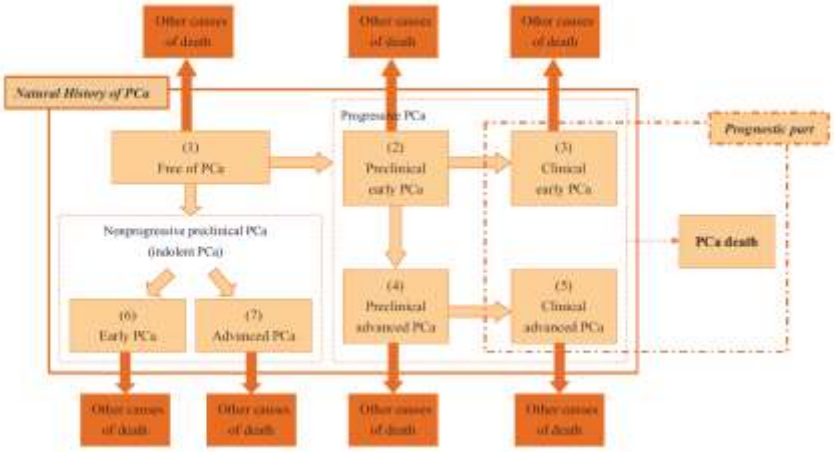
Disease Natural History for Prostate Cancer



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Estimated results of preclinical incidence of progressive and nonprogressive prostate cancer, transition rates and sensitivity using empirical data from Finnish PSA trial

Parameters	Estimates
Preclinical incidence of progressive prostate cancer (λ_P)	
Aged 55–58	0.00128 (0.00099–0.00156)
Aged 59–62	0.00326 (0.00278–0.00375)
Aged 63–66	0.00505 (0.00439–0.00570)
Aged 67–71	0.00774 (0.00689–0.00859)
Preclinical incidence of nonprogressive prostate cancer (λ_{NP})	
Aged 55–58	0.00040 (0.00027–0.00054)
Aged 59–62	0.00061 (0.00042–0.00081)
Aged 63–66	0.00074 (0.00049–0.00098)
Aged 67–71	0.00066 (0.00040–0.00093)
Transition of progressive prostate cancer from PCDP to CP	
Transition rate ($\delta_{1,2}$)	0.1295 (0.0931–0.1660)
Mean sojourn time ($1/\delta_{1,2}$)	7.72 (6.03–10.74)
Sensitivity	
Prevalent screen	42.8% (35.1%–50.6%)
Subsequent screen	59.8% (47.5%–72.0%)

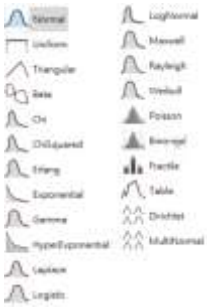
UICC

IJC

Number of screens for overdetection as an indicator of absolute risk of overdiagnosis in prostate cancer screening

Parameters Related to Disease Process for PCa

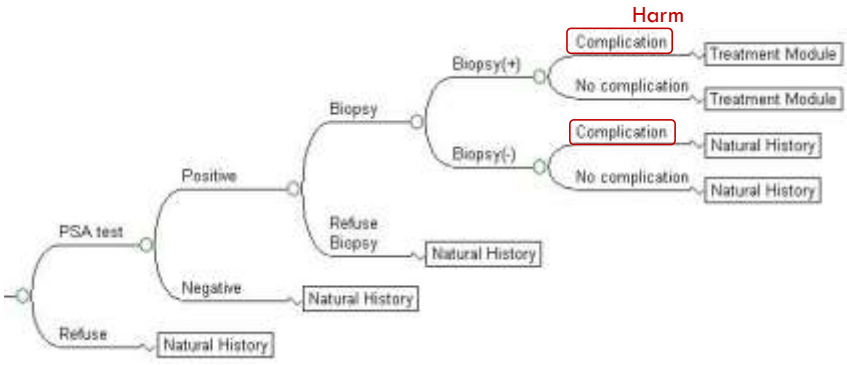
Variable	Base-case estimate	Distribution applied
Prevalence of free of PCa, indolent PCa, preclinical early PCa, preclinical advanced PCa		
At age 55 years	0.969, 0.022, 0.007, 0.001	Dirichlet(77501;1800;587;112)
At age 60 years	0.924, 0.049, 0.023, 0.004	Dirichlet(73910;3935;1805;349)
Annual transition probability from free of PCa to free of PCa, indolent PCa, preclinical early PCa, preclinical advanced PCa, clinical early PCa, clinical advanced PCa, and PCa death (per 100,000)		
At age 55 years	99832, 40, 117, 7, 3, 0, 0	Dirichlet(79866;32;94;6;2;0;0)
At age 60 years	99521, 76, 370, 22, 9, 1, 0	Dirichlet(79617;61;296;18;7;1;0)
At age 65 years	99185, 66, 688, 41, 17, 2, 1	Dirichlet(79348;53;551;33;14;1;0)
At age 70 years	98986, 66, 872, 52, 22, 2, 1	Dirichlet(79189;53;697;41;17;2;0)
Annual transition probability from preclinical early PCa to preclinical early PCa, preclinical advanced PCa, clinical early PCa, clinical advanced PCa, and PCa death (per 1,000)		
All age	844, 106, 43, 6, 1	Dirichlet(844;106;43;6;1)
From preclinical advanced PCa to preclinical advanced PCa, clinical advanced PCa, and PCa death (per 1,000)		
All age	756, 237, 7	Dirichlet(756;237;7)
Case-fatality rate of PCa		
Stage I/II PCa	0.0175	Gamma(139,7935)
Stage III PCa	0.0375	Gamma(149,3968)
Stage IV PCa	0.0916	Gamma(363,3968)
Mortality from other causes		
Age 55-59 years	0.0097	Gamma(2005,206127)
Age 60-64 years	0.0134	Gamma(1996,149366)
Age 65-69 years	0.0196	Gamma(2302,117412)
Age 70-74 years	0.0315	Gamma(2870,91169)
Age 75-79 years	0.0528	Gamma(3796,71905)
Age≧80 years	0.1101	Gamma(6943,63057)



PSA Attendance rate: 65%
Contamination: 20%
Biopsy compliance: 95% ~ Beta(3040, 160)

Markov Decision Tree

Screening and **confirmation** procedures of PSA screening

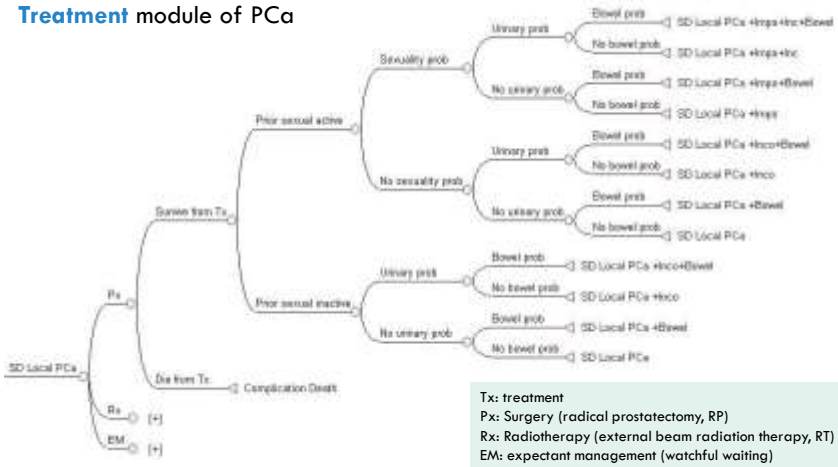


Parameters Related to Screening/Diagnostic Tool

Variable	Base-case estimate	Distribution applied
% of PSA 3.0-3.9 ng/ml	5%	Beta(801,14884)
Sensitivity of PSA testing for early/ advanced PCa	0.86/ 0.95	Beta(2752,448)/ Beta(760,40)
Specificity of PSA testing	0.93	Beta(29847,2153)
Sensitivity of diagnostic methods for early/ advanced PCa	0.64/ 0.99	Beta(2037,1163)/ Beta(798,2)

Markov Decision Tree

Treatment module of PCa



Tx: treatment
Px: Surgery (radical prostatectomy, RP)
Rx: Radiotherapy (external beam radiation therapy, RT)
EM: expectant management (watchful waiting)
Impo: impotence Inco: incontinence
Bowel: rectal injury prob: problem

Parameters Related to Treatment Procedures and Complications

Variable	Base-case estimate	Distribution applied
Treatment choice for early PCa (RP, RT, EM)		
Clinically detected	30%, 60%, 10%	Dirichlet(750;1500;250)
Screen-detected	35%, 40%, 25%	Dirichlet(700;800;500)
% of Stage IV among advanced Pca		
Clinically detected	34.6%	Beta(89, 169)
Screen-detected	20.0%	Beta(23, 91)
Annual rate of initiating active treatment followed EM	5.38%	Gamma(129,2392)
Complication death from treatment (RP/RT)	0.011/0.002	Beta(11,989)/ Beta(2,998)
Prior prevalence of sexual inactive	17.9%	Beta(90,411)
Complications of treatment at initial period (RP/RT)		
Sexual problem	0.47/0.12	Beta(262,295)/Beta(31,227)
Urinary problem	0.28/0.19	Beta(156,401)/Beta(49,209)
Bowel problem	0/0.13	--/Beta(34,224)
Long-term complications of treatment (RP/RT)		
Sexual problem	0.38/0.11	Beta(212,345)/Beta(28,230)
Urinary problem	0.06/0.02	Beta(33,524)/Beta(5,253)
Bowel problem	0/0.06	--/Beta(15,243)

Parameters for Cost (€)

Variable	Base-case estimate	Distribution applied
Screening and Diagnostic		
PSA testing	7.55	Triangular(3.775,15.1)
Free/total PSA	32.7	Triangular(16.3,49)
Diagnostic methods	314	Triangular(112,549)
Biopsy complication	393	Triangular(157,1572)
Staging	344	Triangular(172,344)
Treatment		
Initial cost for early PCa (RP/RT/EM)	9,577/1,9025/2,033	Triangular(4789,19154)/ Triangular(9513,38050)/ Triangular(1017,4066)
Continuous cost (per year) for early PCa (RP/RT/EM)	5,272/8,497/4,593	Triangular(2636,10544)/ Triangular(4249,16994)/ Triangular(2297,9186)
Initial/continuous cost (per year) for Stage III PCa	19,025/8,497	Triangular(9513,28538)/ Triangular(4249,16994)
Initial/continuous cost (per year) for Stage IV PCa	6,885/9,462	Triangular(3443,10328)/ Triangular(4731,14193)
Terminal Cost	13,362	Triangular(3930,27510)
Extra costs due to incontinence (per year)	340	Triangular(170,680)

Parameters for Utility

Variable	Base-case estimate	Distribution applied
Transient utility loss		
Biopsy	-1 day	--
Biopsy Complication	-3 days	--
Initial Treatment for Early PCa (RP/RT)	-35 days/-21 days	--
Initial Treatment for Stage III Pca	-21 days	--
Initial Treatment for Stage IV Pca	-14 days	--
Health state change		
Free of Pca	1.00	--
For non-metastatic Pca		
No complications	0.89	Beta(17,2)
With complications		
Sexual problem	0.84	Beta(22,4)
Urinary problem	0.78	Beta(22,6)
Bowel problem	0.67	Beta(23,11)
Sexual+bowel problem	0.62	Beta(22,14)
Sexual+urinary problem	0.73	Beta(24,9)
Urinary+bowel problem	0.56	Beta(18,14)
Sexual+urinary+bowel problem	0.54	Beta(20,17)
For Stage IV Pca	0.44	Beta(22,28)

Simulated results for various PCa screening strategies

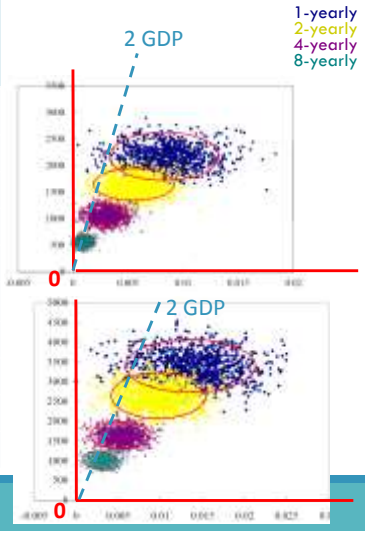
Screening Strategy	RR of PCa death	RR of PCa-related Death	CRO (%)
Start at age 55 years†			
$PSA_{55,1}$	0.87	0.89	2.4
$PSA_{55,2}$	0.92	0.93	2.2
$PSA_{55,4}$	0.96	0.97	1.7
$PSA_{55,8}$	0.99	1.00	1.1
Start at age 60 years‡			
$PSA_{60,1}$	0.87	0.89	4.6
$PSA_{60,2}$	0.92	0.93	4.3
$PSA_{60,4}$	0.96	0.97	3.5
$PSA_{60,8}$	0.99	0.99	2.4

4 % → 3 %

CRO: crude risk of overdetection; **QALY:** quality-adjusted life year. †Compared with CN_{55} ; ‡Compared with CN_{60}.
*Values obtain from a cohort of 100,000 persons who were followed for 25 years with 65% attendance and 20% contamination.
§The screening is less effective and more costly than no screening.

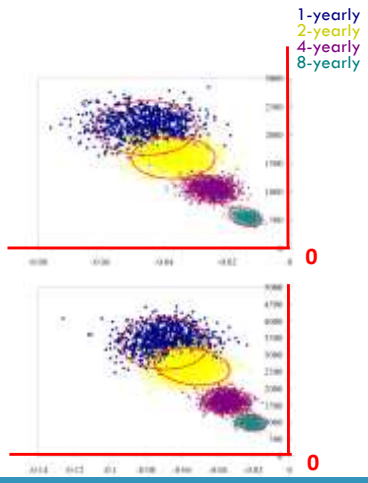
Simulated Results for the Cost-effectiveness Analysis for PCa Screening Strategies (n=100,000)

Screening Strategy	Incremental cost, thousand (€)	Incremental life-year saved, year	Incremental cost (€) / life-years saved
Start at age 55 years†			
$PSA_{55,1}$	588,970	600	588,970
$PSA_{55,2}$	692,220	376	692,220
$PSA_{55,4}$	887,825	179	887,825
$PSA_{55,8}$	2,101,534	33	2,101,534
Start at age 60 years‡			
$PSA_{60,1}$	590,275	1,190	590,275
$PSA_{60,2}$	679,313	790	679,313
$PSA_{60,4}$	815,178	434	815,178
$PSA_{60,8}$	854,873	179	854,873



Simulated Results for the Cost-utility Analysis for PCa Screening Strategies (n=100,000)

Screening Strategy	Incremental cost, thousand (€)	Incremental QALY saved, year	Incremental cost (€) / QALY saved
Start at age 55 years†			
$PSA_{55,1}$	588,970	-4,481	Dominated§
$PSA_{55,2}$	692,220	-3,441	Dominated§
$PSA_{55,4}$	887,825	-2,188	Dominated§
$PSA_{55,8}$	2,101,534	-1,027	Dominated§
Start at age 60 years‡			
$PSA_{60,1}$	590,275	-8,108	Dominated§
$PSA_{60,2}$	679,313	-6,465	Dominated§
$PSA_{60,4}$	815,178	-4,299	Dominated§
$PSA_{60,8}$	854,873	-2,170	Dominated§



Personalized PCa Screening

Multi-state genetic-variant-based model of cancer for individually tailored screening

Step 1: Model Specification

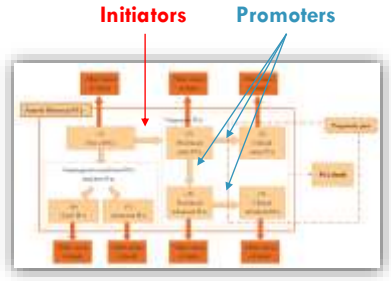
Step 2: Empirical Data
Estimating parameters governing the force of disease progression

Step 3: Mapping
Superimposing generic markers into the evolution of disease natural history

Step 4: Estimation
Converting the susceptibility to occurrence of colorectal cancer obtained from literature to tune the parameters of transition rates from screening data

Step 5: Simulation
Simulating the predicted cumulative life-time risk of oral cancer and oral cancer death

Step 6: Application
Assessing the universal and personalized screening strategies



The effect of selected SNPs on the incidence and aggressiveness of PCa modeled

Incidence of PCa (Free of PCa to Preclinical Early PCa—Initiator

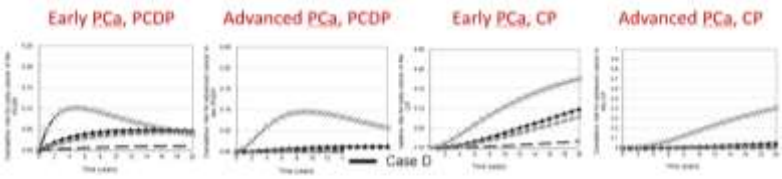
Markers	Position	Associated Allele	% in population	OR
rs4242382	8q24	AA	4.36%	1.75
		GA	30.60%	1.11
rs4430796	17q12	TT(30%)	56.00%	1.38
rs1859962	17q24.3	GG(25%)	50.00%	1.28
rs16901979	8q24(region 2)	AA/CA(7%)	3.00%	1.53
rs6983267	8q24(region 3)	GT/GG(77%)	51.00%	1.37
rs1447295	8q24(region 1)	CA/AA(26%)	14.00%	1.22
rs2660753	3p12	C	11.00%	1.08
rs9364554	6q25	C	28.00%	1.14
rs6465657	7q21	T	47.00%	1.12
rs10993994	10q11	C	39.00%	1.25
rs7931342	11q13	G	50.00%	0.85
rs2735839	19q13	G	15.00%	0.89
rs5945619	Xp11	T	35.00%	1.29
rs5945572	Xp11	A	35.10%	1.23
rs721048	2p15	A	19.00%	1.15
rs10486567	JAZF1 (7)	GG	59.29%	0.74
		GA	35.42%	0.71
			47.60%	1.22
rs138213197	17q21–22	T	2.00%	3.60
Family history			4.60%	1.30

Susceptible gene for overdiagnosis

From Early Preclinical PCa to Advanced PCa or Clinical PCa—Promoter

Markers	Position	Associated Allele	% in population	OR
rs200331695	11q13	A	0.20%	6
IGF-I	Q1			1
	Q2			3.2
	Q3			3.5
	Q4			5.1
IGFBP-3	Q1			5
	Q2			2.5
	Q3			2.5
	Q4			1
rs10486567	JAZF1 (7)	GA vs. AA		1.2
		GG vs. AA		1.18
rs4054823	17p12			1.2
GSTP1 hypermethylation				4.55

Cumulative risk of developing early and advanced PCa in the PCDP and in the CP



- Case A: (Extremely high-risk): 55 years-old; carries risk alleles of rs4242382, HC00813, rs4430796, rs1859962, rs16901979, rs6983267, rs1447295, rs2660753, rs9364554, rs6467657, rs5945572, rs721048, rs10486567, and IVS6-43; fourth quartile IGF levels; IGF-BP in the fourth quartile; rs4054823; GSTP1 hypermethylation; and positive family history
- Case B: (High-risk): 55 years-old; carries risk alleles of rs4242382, rs4430796, rs1859962, rs16901979, rs2660753, rs9364554, rs6467657, rs721048, and rs10486567; third quartile IGF levels; IGF-BP in the third quartile; rs4054823; GSTP1 hypermethylation; and positive family history
- Case C: (Medium-risk): 55 years-old; carries risk alleles of rs4242382, rs4430796, rs1859962, rs16901979, rs2660753, rs721048, and rs10486567; IGF levels in the second quartile, IGF-BP in the third quartile; and rs4054823.
- Case D: (Low-risk): 55 years-old; no risk alleles of the SNPs included in our study; first quartile IGF levels; and IGF-BP in the fourth quartile.

* PCDP: preclinical detectable phase; CP: clinical phase

Risk Score-Based Screening Policies

The 10-year Risk of PCa, the Relative risk, and the Recommend Age to Start Screening by Risk Score Percentiles

Risk percentile	10-year risk for PCa	Relative risk	Start screening age
Non-progressive	6.60%	NA	NA
Susceptible to progressive Pca			
95–100	45.80%	3.1	47
90–95	33.00%	2.23	49
80–90	23.90%	1.62	50
70–80	19.40%	1.31	52
60–70	16.60%	1.12	54
50–60	14.80%	1	55
40–50	13.30%	0.9	57
30–40	11.80%	0.8	58
20–30	10.50%	0.71	60
10–20	9.10%	0.61	62
5–10	7.80%	0.53	65
0–5	6.20%	0.42	NA

Risk Score-Based Screening Policies

The 10-year Risk of Developing Advanced PCa, the Relative Risk, and the Recommend Interscreening Interval by Different Percentiles of Risk Scores Among Subjects Susceptible to Progressive PCa

Risk percentile	10-year risk for advanced PCa	Relative risk	Interscreening Interval
95–100	8.30%	2.82	<1
90–95	6.30%	2.13	<1
80–90	4.70%	1.61	1
70–80	3.90%	1.31	2
60–70	3.30%	1.13	3
50–60	2.90%	1	4
40–50	2.70%	0.91	5
30–40	2.40%	0.81	6
20–30	2.10%	0.72	>6
10–20	1.80%	0.62	>6
5–10	1.60%	0.54	>6
0–5	1.30%	0.43	>6

Conclusions (1)

- The effect of harm on QALY loss may out-weight the life-year gained
- The major QALY loss may come from the utility loss from overdiagnosis cases
- Overtreatment would increase the cost, therefore the PSA screening program is not cost-effective, and reduce the QALY, therefore resulting a dominated result.

Conclusions (2)

- **Applications to Individually Risk Adapted Screening**
  - A shorter interscreening interval/early age of starting screening for the high-risk group can reduce interval cancers.
  - A long interscreening interval/later age of starting screening for the low risk group helps reduce false positive results.
  - Risk score-based approach also considers nonprogressive PCa that would be over-detected if intensive screening policies were offered.

- **Personalized Medical Regime for Screen-Detected Pca**
  - Decisions concerning watchful waiting or radical prostatectomy and whether and how frequently to administer adjuvant therapy, as well as the frequency of clinical surveillance, could be made on the ground of such individual risk score information.