



Prostaatkankerstichting

30 jaar onderzoek naar de effecten van vroege opsporing prostaatkanker

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prostate cancer screening



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The NEW ENGLAND
JOURNAL of MEDICINE



Before we start...

The founders of ERSPC



Fritz Schröder

Louis Denis † 2021



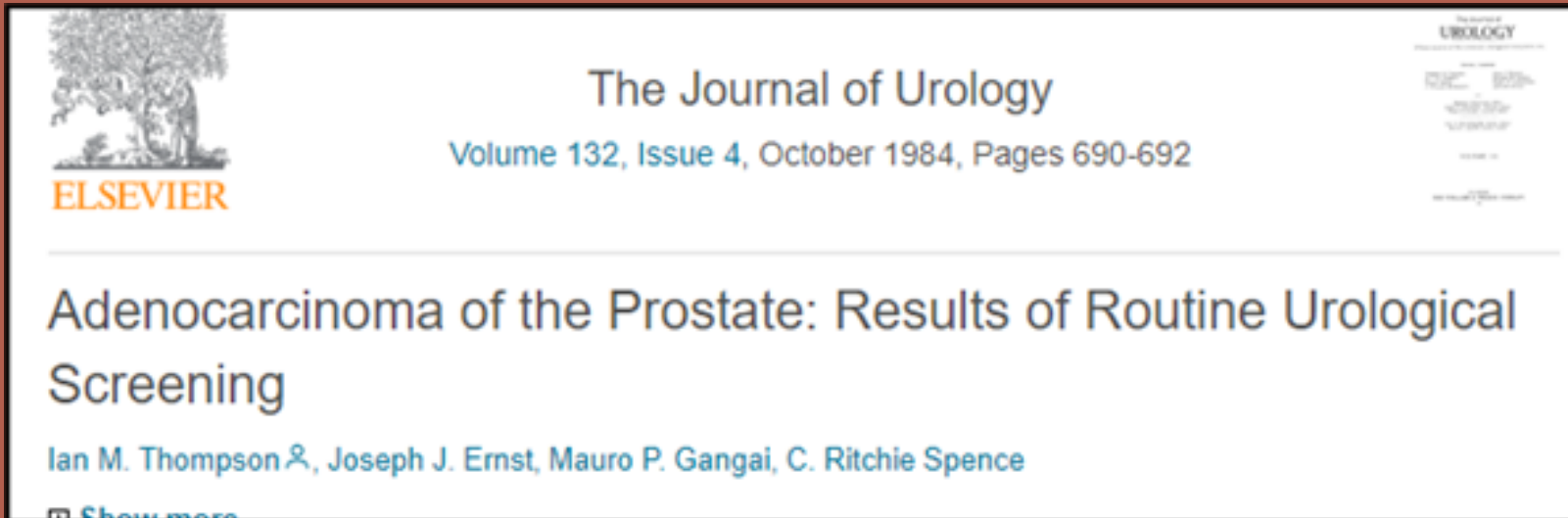
Prostaatkankerstichting

Overview

- **What triggered us to consider screening for PCa?**
- The trials in the 90s
- The results: Benefit!!! Harm.....
- How do we balance it?
- The future

Beyond cure...

- 1984: With the DRE as the only method of diagnosis, 30-35% of men had bone metastases, and 40-45% had nodal disease



The use of adjunctive screening tools for detection of adenocarcinoma of the prostate is suggested.

Then it started

October 8, 1987

N Engl J Med 1987; 317:909-916

DOI: 10.1056/NEJM198710083171501

ORIGINAL ARTICLE ARCHIVE

Prostate-Specific Antigen as a Serum Marker for Adenocarcinoma of the Prostate

Thomas A. Stamey, M.D., Norman Yang, Ph.D., Alan R. Hay, M.D., John E. McNeal, M.D., Fuad S. Freiha, M.D., and Elise Redwine, B.A.

We conclude that PSA is more sensitive than PAP in the detection of prostatic cancer and will probably be more useful in monitoring responses and recurrence after therapy. However, since both PSA and PAP may be elevated in benign prostatic hyperplasia, neither marker is specific. (N Engl J Med 1987; 317:909–16.)

1991, 30 years ago in the NEJM

1156

THE NEW ENGLAND JOURNAL OF MEDICINE

April 25, 1991

MEASUREMENT OF PROSTATE-SPECIFIC ANTIGEN IN SERUM AS A SCREENING TEST FOR PROSTATE CANCER

WILLIAM J. CATALONA, M.D., DEBORAH S. SMITH, PH.D., TIMOTHY L. RATLIFF, PH.D.,
KATHY M. DODDS, R.N., DOUGLAS E. COPLEN, M.D., JERRY J.J. YUAN, M.D., JOHN A. PETROS, M.D.,
AND GERALD L. ANDRIOLE, M.D.

Table 4. Accuracy of Rectal Examination, Serum PSA Measurement, and Ultrasonography in Detecting Prostate Cancer on First Biopsy in 300 Men in the Comparison Group.

MEASURE*	RECTAL EXAMINATION	ULTRASONOGRAPHY	SERUM PSA†
		percent	
Sensitivity	86	92	79
Specificity	44	27	59
Positive predictive value	33	28	40
Negative predictive value	91	91	89
Overall accuracy	58	43	64

We conclude that serum PSA measurement is a useful addition to rectal examination and ultrasonography in the detection of prostate cancer and that it is the most accurate of the three tests for this purpose. Our results suggest that measurement of serum PSA and rectal examination combined, with the addition of ultrasonography in patients with abnormal findings, will provide a better method of detecting prostate cancer than rectal examination alone.

1990

Visiting Professor W. Catalona

Prof. Catalona visits
Erasmus MC Urology
headed by Prof. Schroder.

The basis for an European
screening trial



1991 in Rotterdam

M.J. ROOBOL *ET AL.*

TABLE 1 Characteristics of the screening protocols 1–10

Protocol number	Period	Recruitment rate (%)	Men (N)	Biopsy indication used
1	10/91–01/93	35.6	1 186	DRE and/or TRUS abnormal with lesion ≥ 8 mm. PSA in all men.
2	01/93–03/93	36.5	256	DRE and/or TRUS abnormal with lesion ≥ 8 mm or PSA ≥ 20.0 ng/mL.
3	03/93–05/93	42.4	297	DRE and/or TRUS abnormal with lesion ≥ 8 mm or PSA ≥ 20.0 ng/mL.
4	05/93–11/93	42.4	679	DRE and/or TRUS abnormal or PSA ≥ 4.0 ng/mL.
5	12/93–05/94	40.6	450	DRE and/or TRUS abnormal or PSA ≥ 4.0 ng/mL.
6	06/94–11/95	43.4	8 642	DRE and/or TRUS abnormal or PSA ≥ 4.0 ng/mL.
7	11/95–01/96	53.9	4 147	DRE and/or TRUS abnormal or PSA ≥ 4.0 ng/mL. No screening if PSA < 1.0 ng/mL.
8	03/96–10/96			
8	01/96–03/96	52.8	1 404	DRE and/or TRUS abnormal or PSA ≥ 4.0 ng/mL. No screening if PSA < 1.0 ng/mL.
9	10/96–04/97	50.7	6 000	DRE and/or TRUS abnormal or PSA ≥ 4.0 ng/mL. No screening if PSA < 1.0 ng/mL.
10	05/97–12/99	48.0	21 733	PSA ≥ 3.0 ng/mL. No screening if PSA < 3.0 ng/mL.
Total	Protocol 5–10		42 376	



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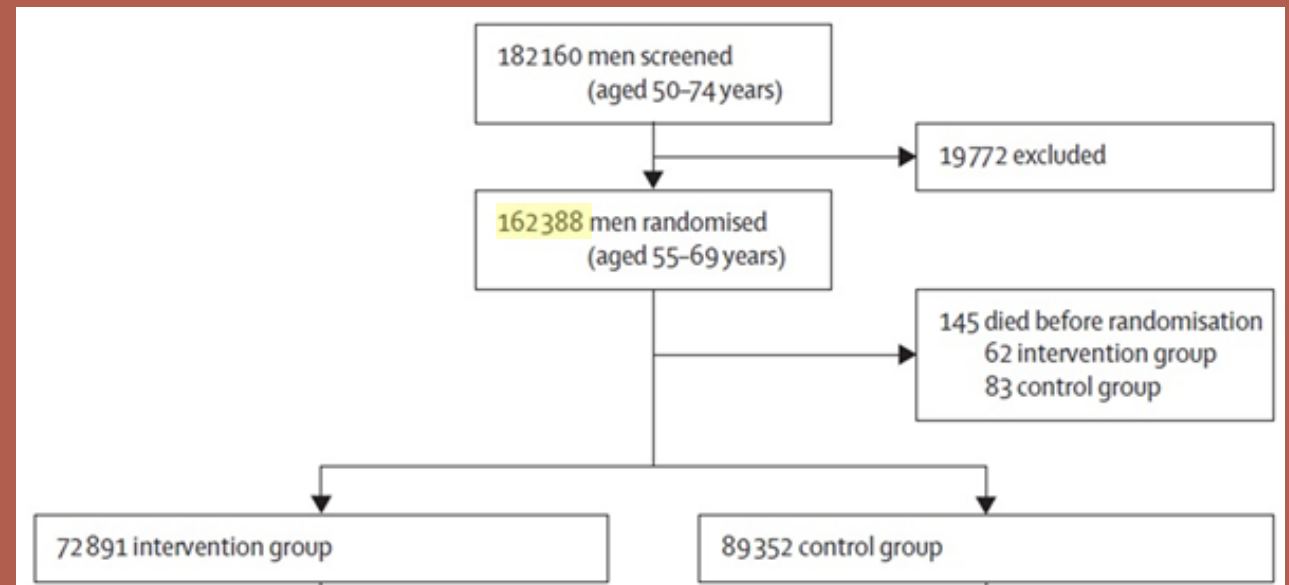
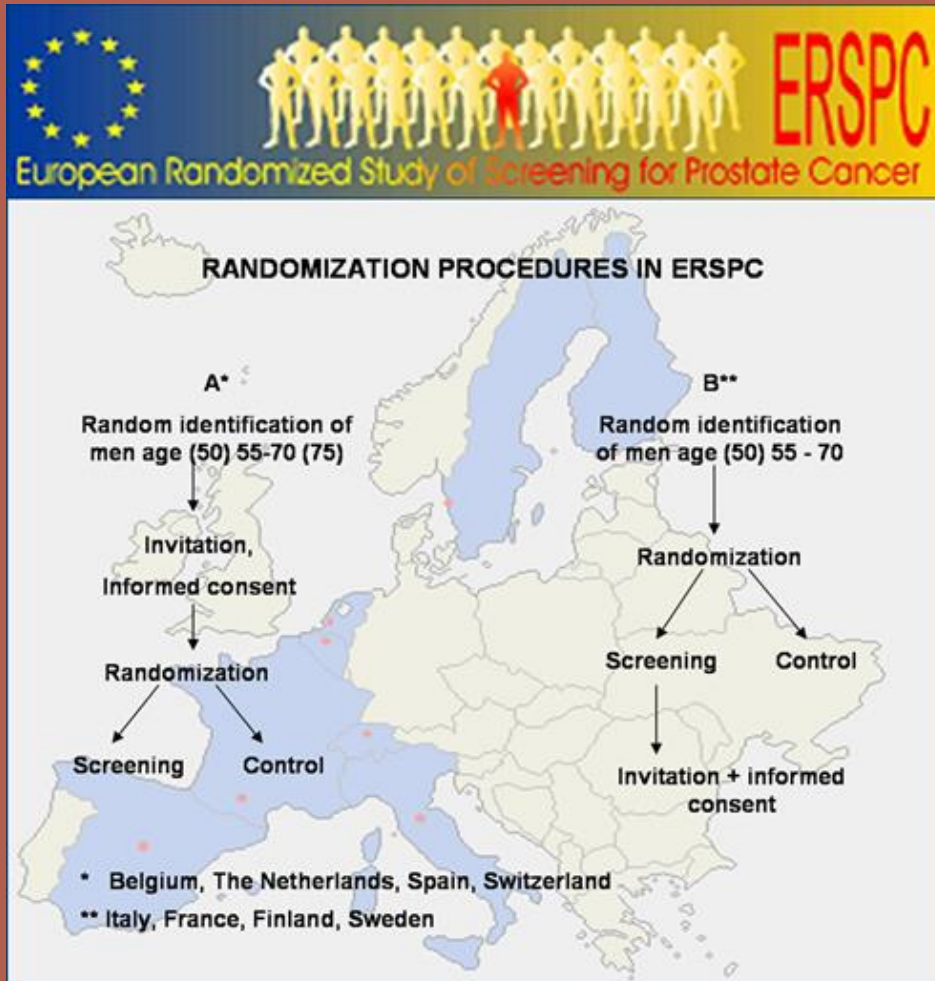
Screening trials initiated in the 90s

Study	Setting, country	Enrolment criteria	Study conducted	No of men randomised (intervention/control)	Screening method	Screening frequency	Primary outcomes	Secondary outcomes
ERSPC (core) ³¹	RCT, multicentre, 9 European countries	Men aged 55-69 years	1993-2003, 13 year follow-up	72 891/89 352	PSA ± DRE. If PSA ≥3 ng/mL standardised prostate biopsy	Screening every 2-4 years	Prostate cancer-specific mortality	All-cause mortality, prostate cancer incidence, clinical stage, quality of life, harms
Labrie (Quebec) ³³	RCT, Quebec, Canada	Men aged 45-80 years	1988-1999, 11 year follow-up	31 133/15 353	PSA ± DRE. If PSA ≥3 ng/mL standardised prostate biopsy	Annual screening	Prostate cancer-specific mortality	Prostate cancer incidence, clinical stage
Lundgren (Stockholm) ²³	RCT, Stockholm, Sweden	Men aged 55-70 years	1988-2003, 20 year follow-up	2400/25 081	PSA, DRE, TRUS. Biopsy depended on DRE and TRUS findings, PSA >10 ng/mL	One-time screening	Prostate cancer-specific mortality	All-cause mortality, prostate cancer incidence
PLCO ³²	RCT, multicentre, US	Men aged 55-74 years	1993-2001, 15 year follow-up	38 340/38 343	PSA, DRE	Annual screening	Prostate cancer-specific mortality	All-cause mortality, prostate cancer incidence, clinical stage, Gleason grade, harms

RCT=randomised controlled trial. PSA=prostate-specific antigen. DRE=digital rectal examination. TRUS=transrectal ultrasound.

To assess the effect of PSA based screening on prostate cancer-specific mortality more than 300,000 men were included in studies

ERSPC



- Screening interval: 4 years in 87%, 2 years in 13% (Sweden)
- Biopsy indication (sextant lateral): PSA \geq 3.0 ng/ml
- Standardized causes of death evaluation
- Quality control by independent committees (e.g. pathology, PSA)

Started in 1993 In 8 European countries
www.erspc.org

PLCO



- From 1993 through 2001, **76,693** men were randomly assigned at 10 U.S. study centers
- They received either annual screening (38,343 men) or usual care as the control group (38,350 men)
- Men in the screening group were offered annual PSA testing for 6 years and digital rectal examination for 4 years.
- Diagnostic evaluation was decided by the patients and their primary physicians.

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Meeting archive

- Copenhagen 12 March, 2018
- Rotterdam 26-27 October 2017
- London 23 March, 2017
- Rotterdam 10 November, 2016
- Munich 10-11 March, 2016
- Schiphol Amsterdam 5 November, 2015
- Madrid 19-20 March, 2015
- Schiphol Amsterdam 23 October, 2014
- Antwerp March 27-28, 2014
- Lille 7-8 November, 2013
- Marstrand 11-12 April, 2013
- Ripley, Harrogate 7-9 November, 2012
- Ylläsjärvi 29-30 March, 2012
- Toulouse 3-4 November, 2010
- Zuoz 2-3 March, 2010
- Nyon 13-14 October, 2009
- Gothenburg 16-17 April, 2009
- Seili 22-24 October, 2008
- Toledo 15-16 March, 2007

Results..... Debate, debate and debate....



ERSPC:

- Rate ratio for death from prostate cancer in the screening group, as compared with the control group, was 0.80 (95% CI: 0.65 to 0.98)
- Reduction in M+ advanced disease 30-40% (Eur Urol 2012)

And clarity

Reevaluating PSA Testing Rates in the PLCO Trial

TO THE EDITOR: In March, the Centers for Medicare and Medicaid Services temporarily suspended the development of a proposed “Non-Recommended Prostate-Specific Antigen (PSA)-Based and why the test was performed. Categorical responses for when the most recent test was performed were within the past year, 1 to 2 years ago, 2 to 3 years ago, more than 3 years ago, and

Annals of Internal Medicine

ORIGINAL RESEARCH

Reconciling the Effects of Screening on Prostate Cancer Mortality in the ERSPC and PLCO Trials

Tsodikov et al. 2017

Conclusion: After differences in implementation and settings are accounted for, the ERSPC and PLCO provide compatible evidence that screening reduces prostate cancer mortality.

Confirmation of results: harm < > benefit



ERSPC:

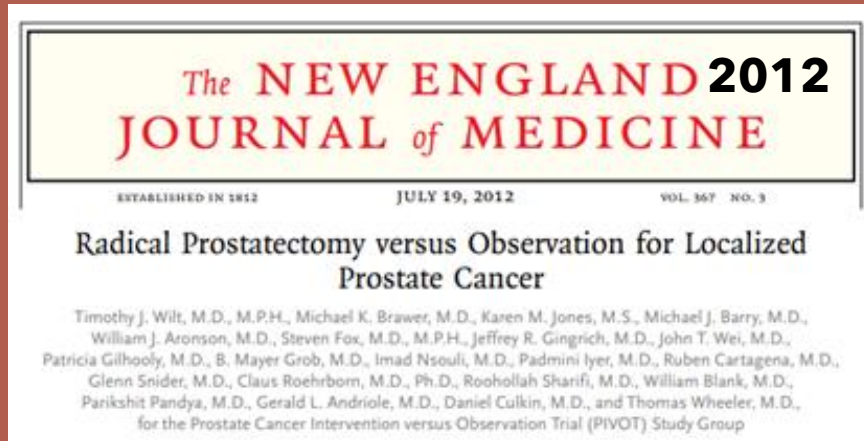
- Rate ratio for death from prostate cancer in the screening group, as compared with the control group, was 0.79 (95% CI: 0.68 to 0.91)



Adjusting for harm:

- The benefit of screening was diminished by loss of QALYs owing to postdiagnosis long-term effects (**overdiagnosis and subsequent overtreatment**)

Should we treat all screen-detected PCa?

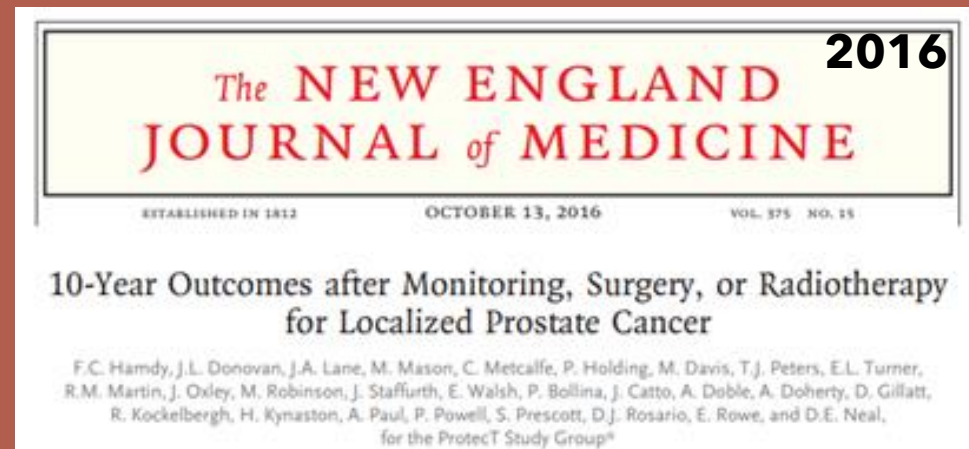


Among screen detected localized PCa, radical prostatectomy did not significantly reduce all-cause or prostate-cancer mortality, as compared with observation, through at least 12 years of follow-up.

No, certainly not , **Active Surveillance** is the way to go

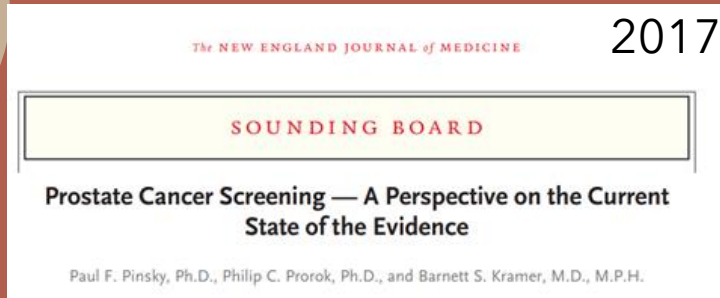
Even better:

AVOID the diagnosis and stop making men cancer patients

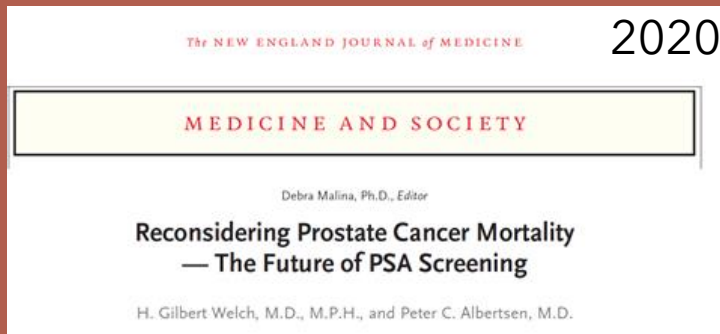


At a median of 10 years, prostate-cancer-specific mortality was low irrespective of the treatment assigned, with no significant difference among treatments.

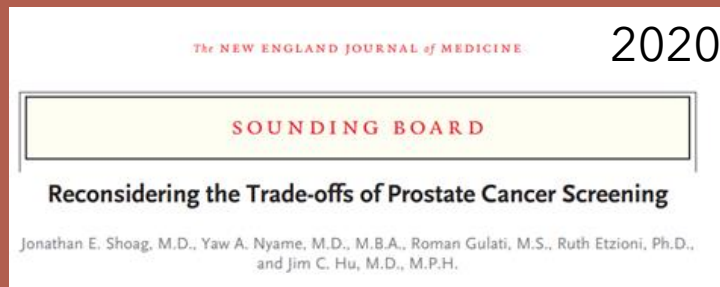
Reflection on what we had learned..



There is a critical need for strategies to reduce the burdens associated with the diagnosis of **indolent disease**, through a combination of **not diagnosing** it in the first place and accurately classifying it as **not needing any further follow-up or treatment**, while still maintaining any mortality benefits for men with aggressive disease. Perhaps that is the **most pressing research challenge** going forward.

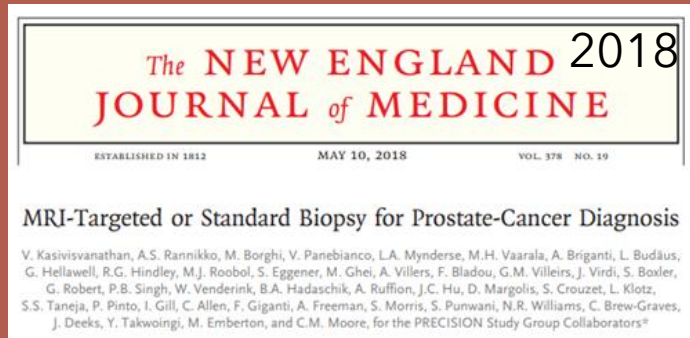


We have learned that the conventional goal of screening – to maximize cancer detection – is wrong. The appropriate goal is more complex: **identify the few cancers that matter**, while not disturbing the rest of the population.

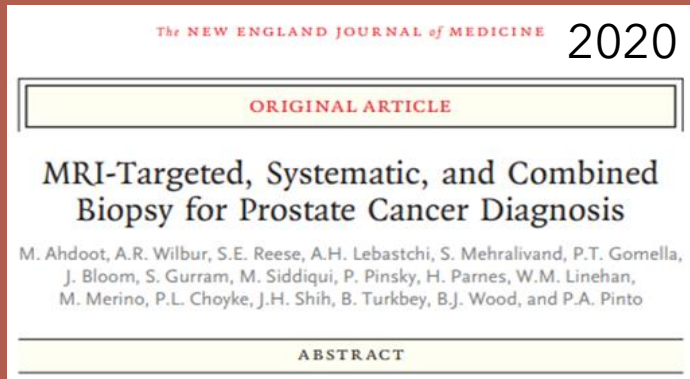


Based on long-term FU and **new developments**: As clinicians who screen, diagnose, and treat patients with prostate cancer and as statisticians who are devoted to understanding the effects of cancer screening, we suggest that the **balance of benefits and harms of screening may be more favorable than is generally appreciated.**

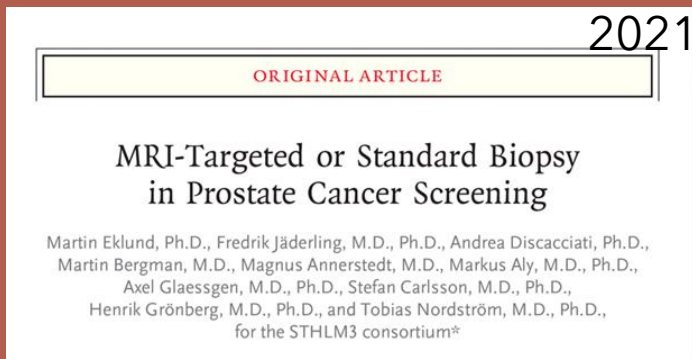
mpMRI in clinical and screening setting



PRECISION trial: MRI, with or without targeted biopsy, led to **fewer men undergoing biopsy**, more clinically significant cancers being identified, **less overdetetection of clinically insignificant cancer**, and fewer biopsy cores being obtained than did standard transrectal ultrasonography-guided biopsy.



Among patients with MRI-visible lesions, **combined biopsy** led to more detection **of all** prostate cancers. However, MRI-targeted biopsy alone **underestimated** the histologic grade of some tumors.



STHLM3MRI trial: MRI with **targeted and standard biopsy** in men with MRI results suggestive of prostate cancer was noninferior to standard biopsy for detecting clinically significant prostate cancer in a population-based screening-by-invitation trial and resulted in **less detection of clinically insignificant cancer**.

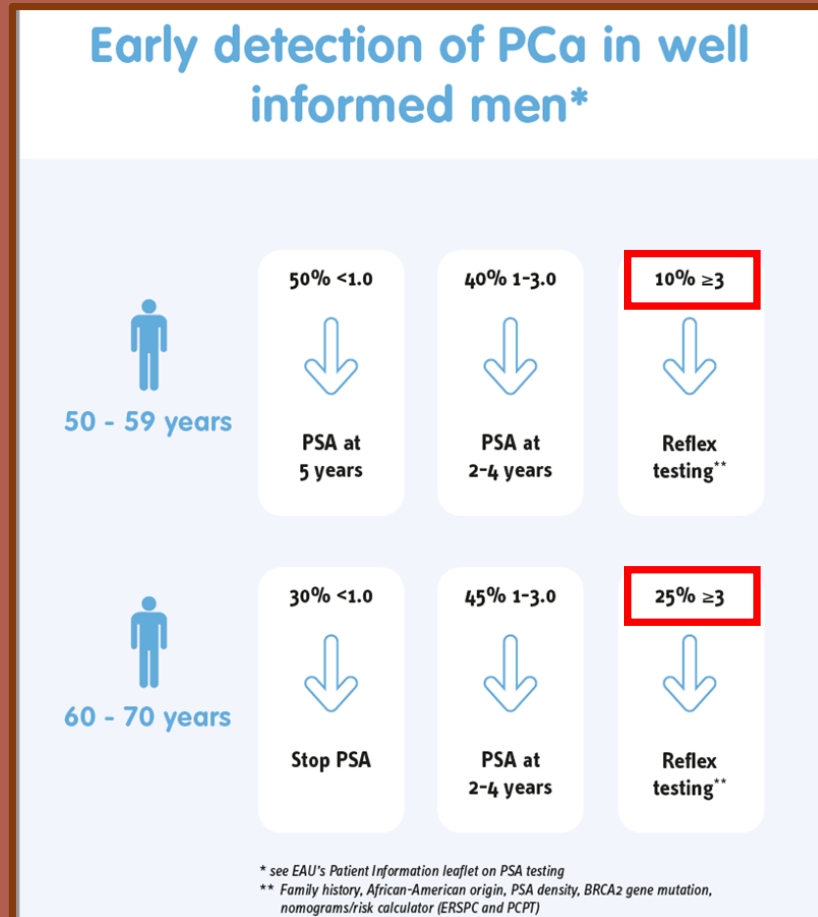


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Population based screening



12,750 men enrolled → 1,532 randomized with PSA ≥ 3 ng/ml

STHLM3MRI trial : 12% directly referred for mpMRI

Proportion MRI-negative correlates to disease risk distribution

	STHLM3MRI Main Study n=1,532	Göteborg-2 n=551	Precision n=500	MRI-First n=251	STHLM3MRI Phase 1 n=532
Cohort	Screening	Screening	Clinical	Clinical	Clinical
Age, yrs (median)	66	57	64	64	64
PSA, ng/ml (median)	4.3	3.3	6.7	6.5	6.3
MRI not suggestive of significant cancer	56%	77%	28%	21%	19%

In Europe: 55 Million men aged 55-75 yr, with a PSA cut-off as only risk stratification step:
6.6 Million men eligible for MRI , 60% unnecessary?



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Trials, trials, trials.

- Prostate cancer screening is a dynamic field of research

- What are we waiting for?

Table 1 - Overview of the ongoing or recently completed trials related to risk-stratified early detection of prostate cancer

Trial Name Trial number Country Principal Investigator	Design	Study period	N	Age at inclusion (yrs.)	Methods for risk adaption per arm	Biopsy indication	Primary endpoint
PROBASE [1, 2] ISRCTN37591328 Germany Peter Albers	RCT, Multicenter	2013-2028	46.000 (target)	a. 45 b. 50	a. PSA at 45 yrs.* b. PSA at 50 yrs.* *mpMRI if PSA ≥3	a/b. PSA ≥3* *SBx and TBx if mpMRI is positive	Incidence of metastatic PCa after 15 yrs.
Göteborg prostate cancer screening 2 (G2) trial [1, 3] ISRCTN94604465 Sweden Jonas Hugasson	RCT, Single center	2015-2040	40.000 (target)	50-60	a. PSA + mpMRI if PSA ≥3 b. PSA + mpMRI if PSA ≥3 c. PSA + mpMRI if PSA ≥1.8	a. PSA ≥3 (SBx + TBx*) b. PSA ≥3 (TBx only*) c. PSA ≥1.8 (TBx*) *If mpMRI is positive (PI-RADSv2 3-5)	PCa detection rate and overdiagnosis (small insignificant PCa).
STHLM3-MR 2 [4-6] NCT03377881 Sweden Tobias Nordström	RCT, Multicenter	2018-2020 (completed)	12.750 (actual)	50-74	a. PSA + STHLM3 test + bpMRI if PSA ≥3 b. PSA + STHLM3 test + bpMRI if PSA ≥1.5 and S3M >11%	a. PSA ≥3 b. STHLM3 test ≥11% and PSA ≥1.5 *SBx and/or TBx according to positive bpMRI (PI-RADSv2 3-5) and STHLM3	Detection rate of csPCa (GS ≥7).
PROSCREEN [4, 7] NCT03423303 Finland Anssi Auvinen	RCT	2018-2028	67.000 (target)	50-63	a. PSA + 4Kscore when PSA ≥3 + mpMRI when increased risk b. No screening	a. PSA ≥3 and abnormal 4Kscore and positive mpMRI	PCSM after 10 yrs.
PROSTAGRAN [1, 8] ISRCTN43502108 United Kingdom David Eldred-Evans	Observational, prospective, multicenter	2018-2019 (completed)	408 (actual)	50-69	a. PSA + TRUS + bpMRI	a. Any positive test result* *PSA ≥3, bpMRI/TRUS ≥PI-RADS 3-5 or 4-5	Proportion positive MRI and TRUS.
Nanjing [4, 9] NCT04322045 China Jingyan Shi	Interventional (Clinical Trial), single group	2020-2022	10.000 (target)	≥50	a. PSA + mpMRI if PSA ≥4	a. Positive mpMRI (PI-RADSv2 3-5)	Incidence of PCa.
MVP (MRI vs PSA) [4] NCT02799303 Canada (Toronto) Robert Nam	RCT	2016-2020	1010 (target)	≥50	a. mpMRI b. PSA	a. positive mpMRI b. PSA ≥4	csPCa (GS ≥7 on TRUS biopsy).
ReIMAGINE [4, 10] NCT04063566 United Kingdom Caroline Moore	Interventional (Clinical Trial), single group	2019-2022	300 (target)	50-75	a. PSA + mpMRI	a. positive mpMRI or PSA density ≥0.12	1. Acceptance rate of invitation for screening. 2. Prevalence of positive MRI. 3. Prevalence of PCa.
VISIONING1 [4] NCT03749993 Switzerland Cyrill Rentsch	Interventional (Clinical Trial), single group	2019-2023	500 (target)	46-75	a. bpMRI + PSA	a. positive bpMRI (PI-RADS 3-5) (TBx ± SBx*) *SBx if PSA >10 or suspicious DRE	Total costs of MRI based PCa screening.
PROFILE study [4, 11] NCT02543905 United Kingdom Rosolind A Eeles	Observational, prospective	2015-2025	700 (target)	40-69 (at higher genetic risk)	a. PSA + mpMRI	a. all participants	Association of genetic profiles and biomarkers to predict PCa.
BARCODE – 1 Study [4] NCT03857477 United Kingdom Rosolind A Eeles	Observational, prospective, Multicenter	2019-2027	5000 (target)	55-69	a. SNP profile + mpMRI to men within the top 10% genetic risk score profile	a. the top 10% genetic risk score profile (follow-up benign biopsy result by PSA)	Association of SNP profile and PCa.
PreCaRis Study [4, 12, 13] NCT01739062 Denmark Jacob Fredsøe	RCT, Multicenter	2013-2019 (completed)	7800 (actual)	18-80	a. PSA + SNP test b. PSA	–	Number of low-risk patients who get a PSA test.
PCa Screening in Men With Germline BRCA2 [4] NCT02154672 United States of America Preston Sprenkle	Observational, prospective	2014-2018 (completed)	100 (actual)	30-90 (BRCA2 mutation carriers)	a. PSA + DRE + mpMRI if either is abnormal	a. positive PSA and/or DRE and/or mpMRI	Incidence of PCa among male BRCA2 mutation carriers.
IMPACT study [4, 14, 15] NCT00261456 United Kingdom Rosolind A Eeles	Observational, prospective	2005-2030	1700 (target)	40-69 (BRCA1/2 mutation carriers)	a. BRCA1/2 carriers* b. BRCA1/2 non-carriers* *PSA + 4Kscore when PSA ≥3	a. PSA >3 b. PSA >3	Incidence of PCa among BRCA 1/2 mutations carriers and non-carriers
PCa Screening Among Men With High Risk Genetic Predisposition [4, 16, 17] NCT02053805 Israel David Margel	Interventional (Clinical Trial), single group	2014-2019 (completed)	188 (actual)	40-70 (BRCA1/2 mutation carriers)	a. PSA + mpMRI	a. Abnormal PSA* mpMRI and/or positive mpMRI** *age-specified PSA criteria ** PI-RADSv2 3-5	Prevalence of PCa among male BRCA 1/2 mutation carriers.

N = number of participants; RCT = randomized controlled trial; PSA = prostate-specific antigen in ng/ml; mpMRI = multiparametric Magnetic Resonance Imaging; PCa = prostate cancer; SBx = systematic prostate biopsy; TBx = targeted biopsy; PI-RADSv2 = Prostate Imaging Reporting and Diagnostic System version 2; STHLM3 test = Stockholm3 test; csPCa = clinically significant PCa; 4K score = Prostate-Specific kallikrein; PCSM = prostate cancer-specific mortality; TRUS = Transrectal ultrasound; bpMRI = biparametric Magnetic Resonance Imaging; DRE = digital rectal examination; SNP = single-nucleotide polymorphism; BRCA = Breast Cancer gene

30 years of knowledge brought together

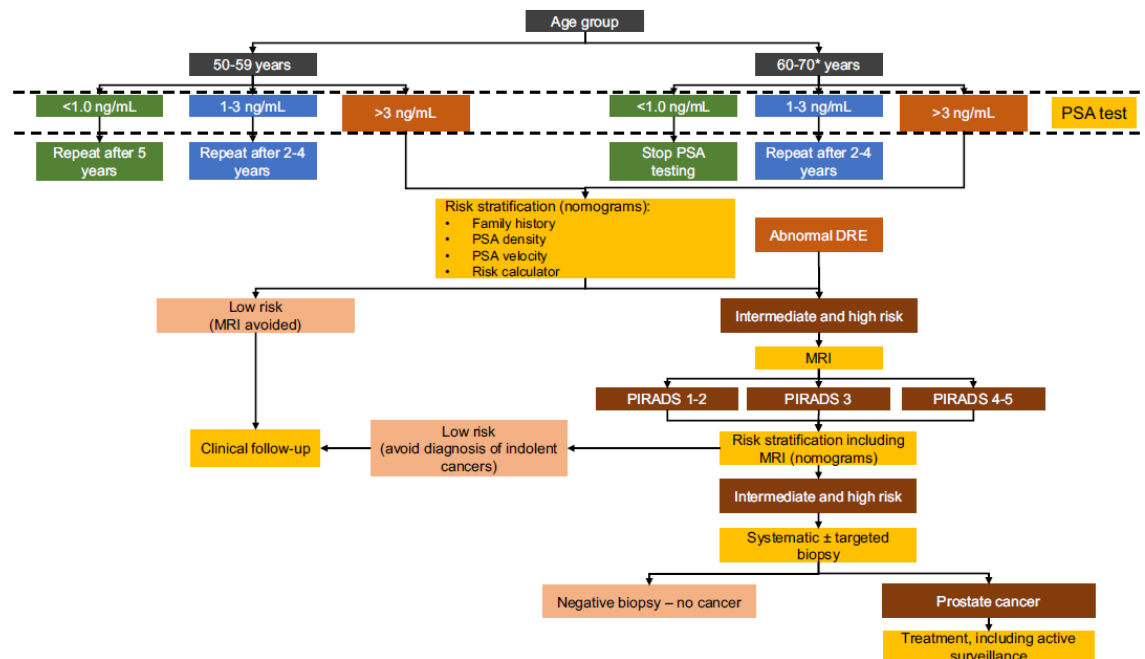
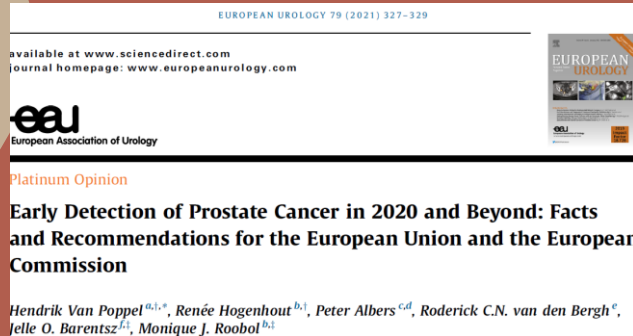


Fig. 4 – Risk-adapted algorithm for the early detection of prostate cancer, adapted based on prostate cancer guidelines published by the EAU [21]. The patient's values and preferences should always be taken into account as part of a shared decision-making process [21]. DRE = digital rectal examination; EAU = European Association of Urology; MRI = magnetic resonance imaging; PIRADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen.

*Healthy men >70 yr without important comorbidities and a life expectancy of >10-15 yr may continue PSA testing.

- 30 years have passed
- We have learned so much
- Isn't it time we implement our knowledge in an organized way accessible for all men in Europe?

Why Urology ? why Prostate Cancer?

- The text from my inaugural address:
- **Why urology?**
- Not the most appealing subject to talk about at a birthday party, unless it is a joke....
- Just because urological problems are not or rarely discussed it is a fascinating part of medicine.
- In particular, **prostate cancer** often has **a long-lasting considerable impact on daily life**.
- Patients often **suffer in silence** and feel they are **alone**
- To help these men is a privilege
- *Working at the department of Urology since September 1991.*

Thank you for listening

