Universitätsspital Basel 2024-01-12

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Novel strategies for prostate cancer screening – the Stockholm trials

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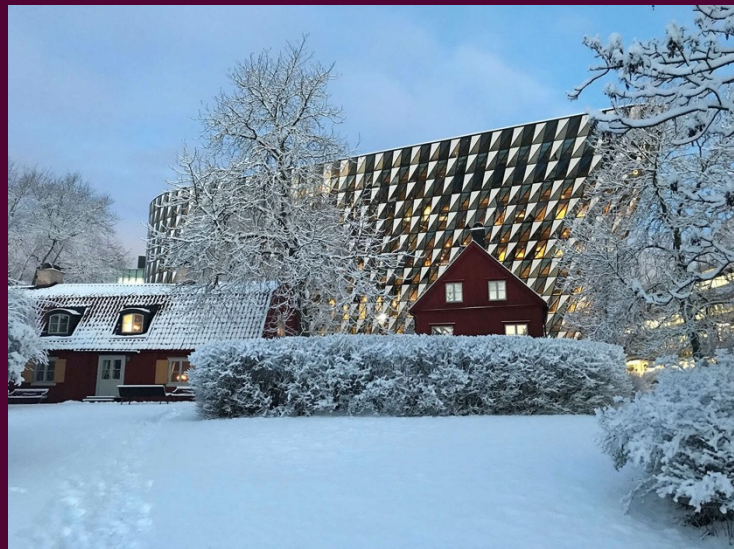


High mortality and national trial data – Reason for high interest for PC testing in Sweden?

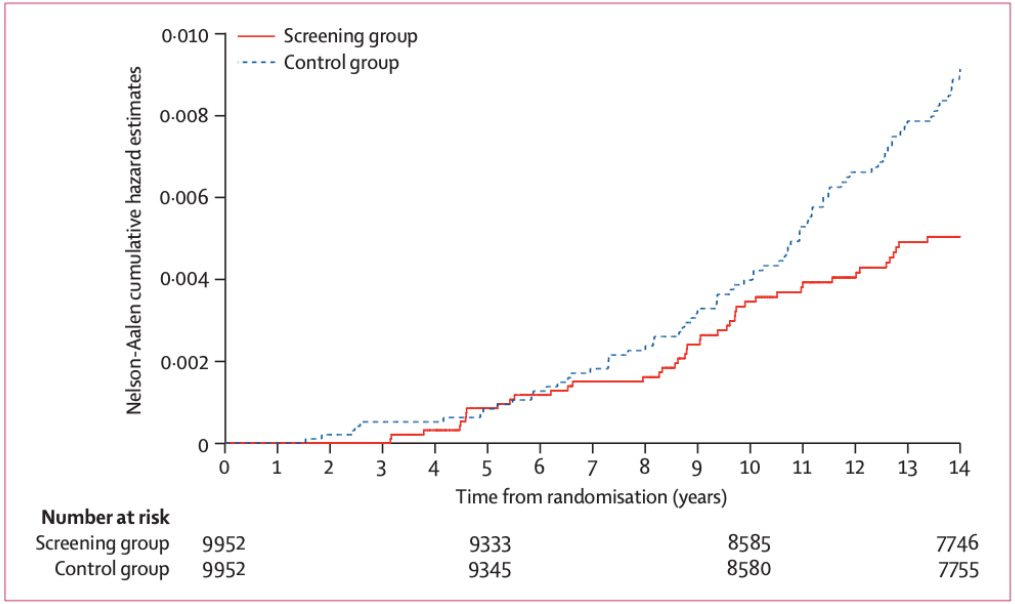


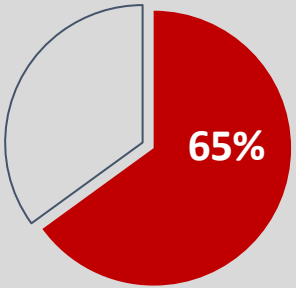
Figure 3: **Cumulative risk of death from prostate cancer using Nelson-Aalen cumulative hazard estimates**

≈ halved prostate cancer mortality

Göteborg1 trial: Jonas Hugosson et al Lancet Onc 2010

Opportunistic testing is common, also in men not benefitting

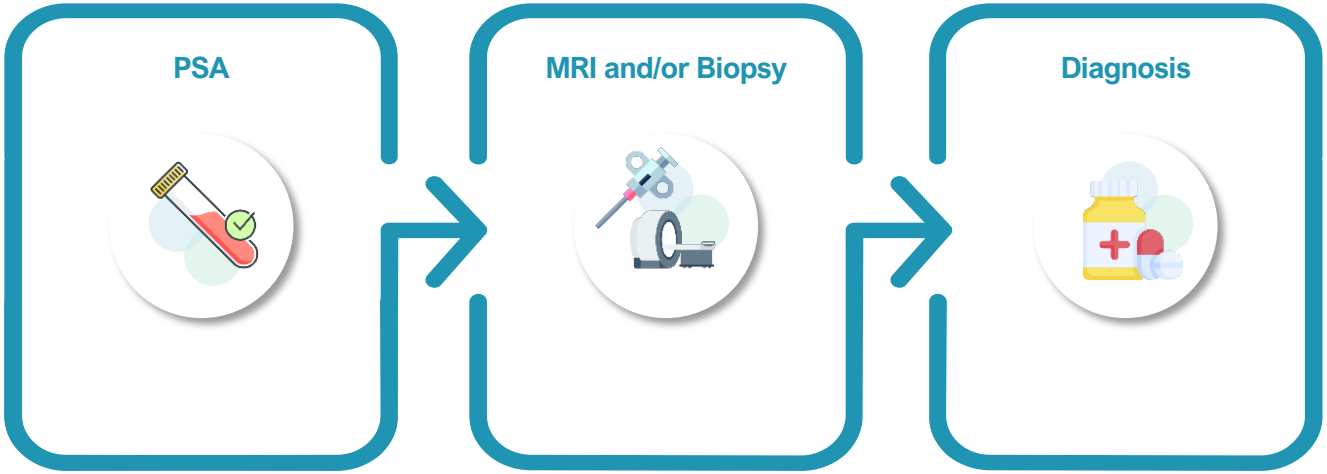
High level of unstructured testing



65% of men aged 50-69 were tested within 5 years

Prostate-specific antigen (PSA) testing is prevalent and increasing in Stockholm County, Eur Urol 2013

Current diagnostic chain for early detection of prostate cancer



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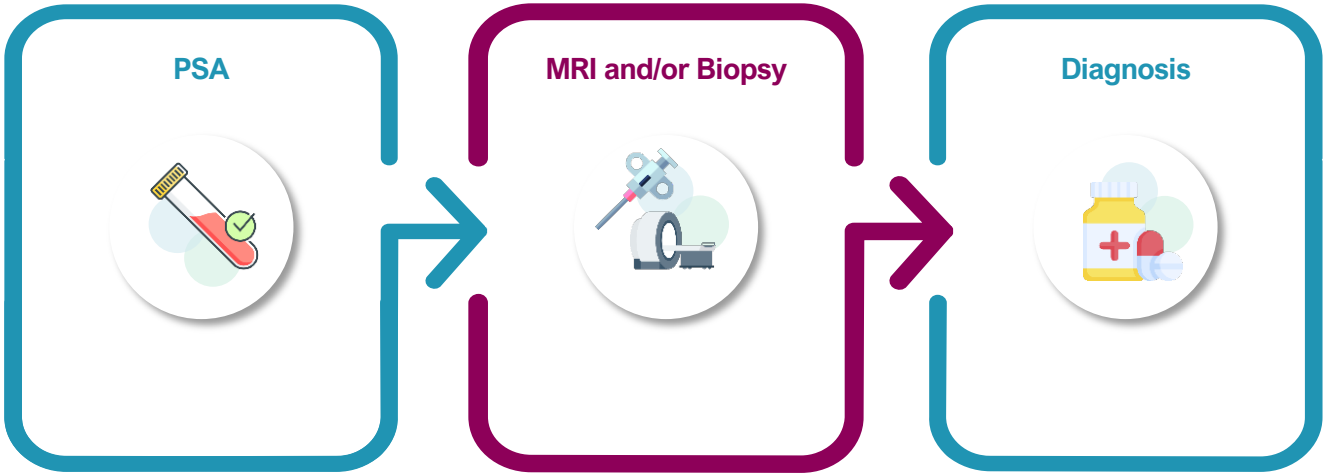
Current diagnostic chain for early detection of prostate cancer



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STHLM3 MRI is a screen-by-invitation paired and randomized study

49,118
invited
50-74 yrs

12,750
participants

Analysis of PSA & Stockholm3

2,293
Randomized 2:3
PSA≥3 | S3≥0.11

R

Standard biopsy

MRI + biopsy (if MRI-positive)

MRI: 1.5/3T, 16 minutes protocol without DCE
Biopsies: 3-4 targeted bx to PI-RADS≥3 (bkFusion), standard bx included 10-12 bx to the dorsal prostate, 3 providers
Pathology: centralized (ISUP 2014)

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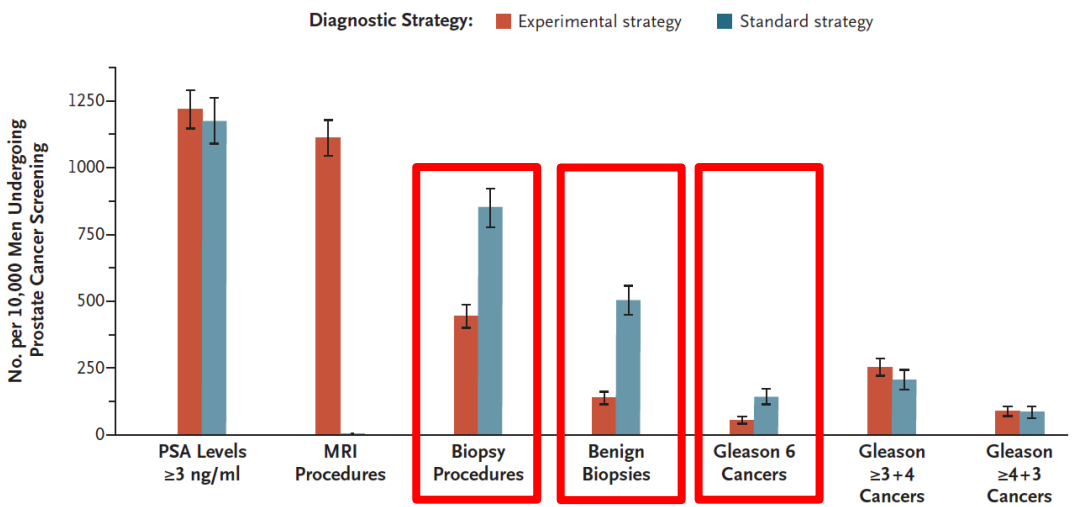
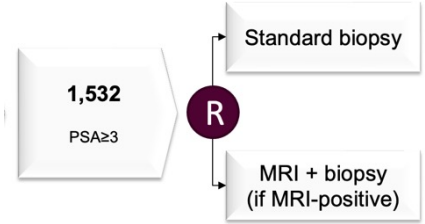
Biopsies in bpMRI-positive men maintains detection of significant cancer, decreases overdetection and biopsy numbers also in screening



	PSA Levels ≥3 ng/ml	MRI Procedures	Biopsy Procedures	Benign Biopsies	Gleason 6 Cancers	Gleason ≥3+4 Cancers	Gleason ≥4+3 Cancers
Experimental Strategy — no.	1221	1112	444	138	54	252	88
Standard Strategy — no.	1175	2	853	504	142	206	84
Absolute Difference (95% CI) — percentage points	0.5 (−0.7 to 1.6)	—	−4.1 (−5.0 to −3.2)	−3.7 (−4.3 to −3.0)	−0.9 (−1.2 to −0.5)	0.5 (−0.1 to 1.0)	0.0 (−0.3 to 0.4)
Relative Difference (95% CI)	1.04 (0.94 to 1.14)	—	0.52 (0.45 to 0.60)	0.27 (0.22 to 0.34)	0.38 (0.26 to 0.55)	1.22 (0.97 to 1.55)	1.05 (0.72 to 1.54)



Eklund et al. New Engl J Med 2021

High proportion negative MRIs in screening cohorts

	STHLM3MRI	Göteborg-2	OPT Sweden
Median age (yrs)	61	56	50
Number of MRIs	846	765	645
PI-RADS 1-2	**62%**	**64%**	**63%**
PI-RADS 3	21%	8%	21%
PI-RADS 4	10%	20%	10%
PI-RADS 5	8%	7%	5%

Eklund et al. New Engl J Med 2021, Hugosson et al New Engl J Med 2022, Bratt et al Eur Urol 2023

Systematic biopsy in MRI-positive captures majority of significant cancers*

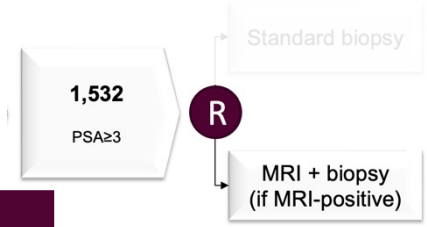
Very few MRI-negative men needs biopsy

*Disease verification by only systematic biopsies
62% negative MRIs

Biopsy outcome in men with PSA≥3ng/ml	**Syst. bx in MRI+** (MRI-arm) n = 929	**Syst bx in all** (Standard arm) n = 603	**Difference** (95% CI)
Detection of clinically significant cancer (Gleason Score ≥ 7)	**16%** (144/929)	**18%** (106/603)	-2.1% (-5.9% to 1.7%)
Detection of clinically insignificant cancer (Gleason score 6)	**6%** (58/929)	**12%** (73/603)	-5.9% (-8.9% to -2.8%)

Unpublished data

Systematic biopsies should not be performed in all, jury still out for adding them in MRI-positive men?

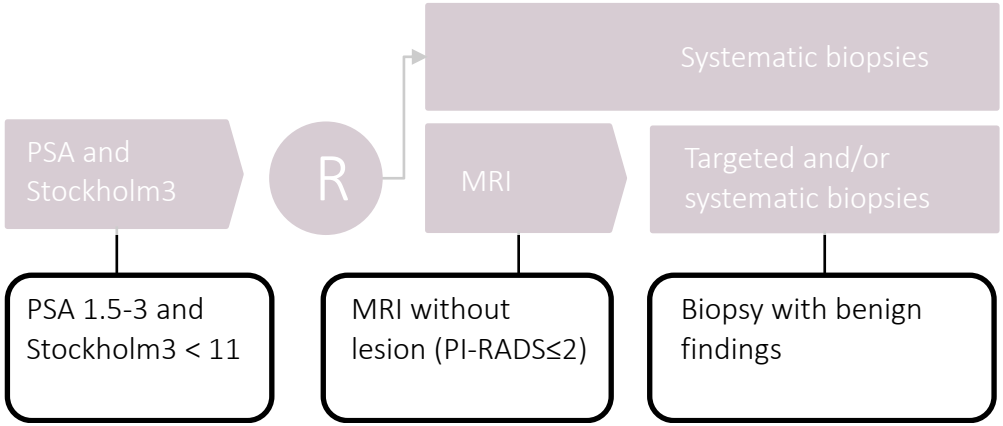


Biopsy strategy in PI-RADS ≥3 (n=929)	ISUP 1	ISUP ≥2	ISUP ≥3
Target bx	2% (n=23)	17% (n=162)	6% (n=55)
Target + systematic bx	4% (n=41)	21% (n=192)	7% (n=67)

1.7 delayed ISUP ≥2 cancer per saved ISUP 1
if **omitting syst biopsies in MRI-positive men**
-> keep systematic biopsies in MRI-positive?

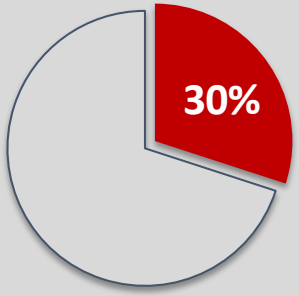
Eklund et al. New Engl J Med 2021

Need to identify adequate re-screening protocols



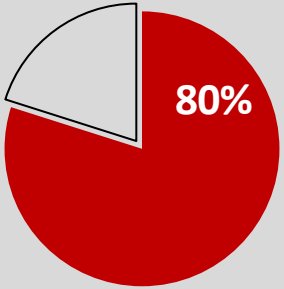
Re-screening using PSA and MRI at 2-3 years, more questions than answers

Men re-classify to PSA≥3



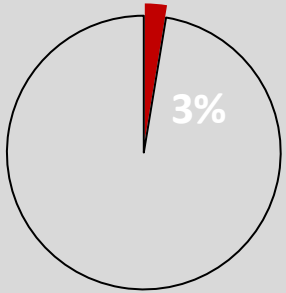
30% (n=326/1094) of men with PSA 1.5-2.9 had PSA ≥3 at re-screen

Many MRI lack lesions



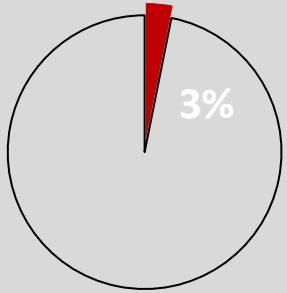
80% (n=533/667) of MRIs negative

Very few new MRI-lesions



3% (n=10/383) PI-RADS ≥4 if previous negative MRI

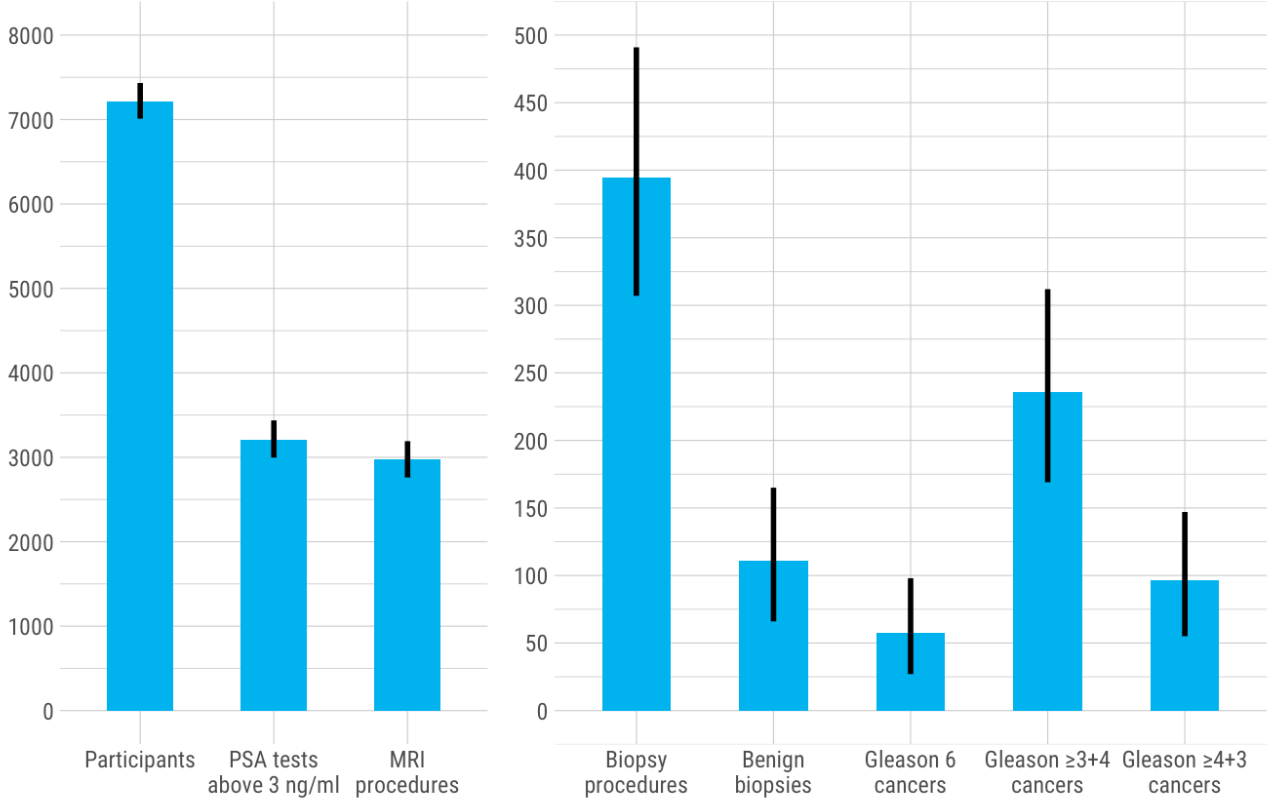
Limited cancer detection



3% (n=48/1500) ISUP ≥2 in re-screened (1%/n=12 ISUP ≥3)

Nordström et al EAU 2023; submitted

Number of participants, elevated PSA tests, performed procedures and detected cancers per 10,000 men invited to a second screening round



Participation rate 72%

MRIs
- ≈40 MRIs per 100 participants
- 80% negative MRIs
- Stable predictive value of MRI

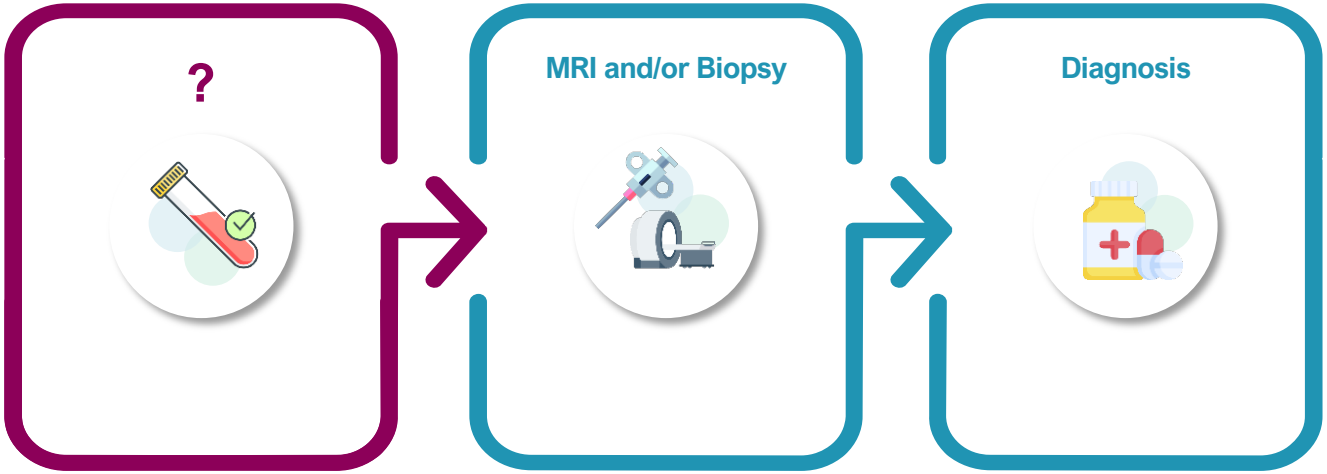
Biopsy procedures
- 5 per 100 participants
- Half of biopsies Gleason ≥7

Cancer detection in participants
- Gleason 6: 0.7%
- Gleason ≥7: 3%
- Gleason ≥4+3: 0.8%

Nordström et al EAU 2023; submitted

- Organised early detection can
  - → reduce prostate cancer mortality
  - → reduce harmful testing
- MRI maintains sensitivity and decreases detection of low-grade tumors
- High consumtion of MRI in screening setting
- Yet unclear how to optimize re-screening and stop age

Current diagnostic chain for early detection of prostate cancer



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PSA has well-known limitations

Low sensitivity

30–50%

of aggressive cancers are missed by PSA[1]

Low specificity

70–80%

false positives from PSA[2]

Source: 1) Thompson et al. Effect of Finasteride on the Sensitivity of PSA for Detecting Prostate Cancer. Journal of the National Cancer Institute. 2016. 2) Grönberg et al. Prostate cancer screening in men aged 50–69 years (STHLM3): a prospective population-based diagnostic study. Lancet Oncology. 2015. Grönberg et al. Prostate Cancer Diagnostics Using a Combination of the Stockholm3 Blood Test and Multiparametric Magnetic Resonance Imaging. European Urology. 2018.

Stockholm3 combines proteins, genetics and clinical data into an easy to interpret result

Plasma concentration of total and free PSA, PSP94, GDF15, and KLK2

Genotyping information (101 SNPs)

Clinical patient data (age, family history of prostate cancer, previous biopsies, use of 5-alpha reductase inhibitors)

Stockholm3 test = f [PROTEINS + GENETICS + CLINICAL DATA] →

Elevated risk
Stockholm3 Risk Score ≥ 11

Normal risk
Stockholm3 Risk Score 4-10

Low risk
Stockholm3 Risk Score ≤ 3

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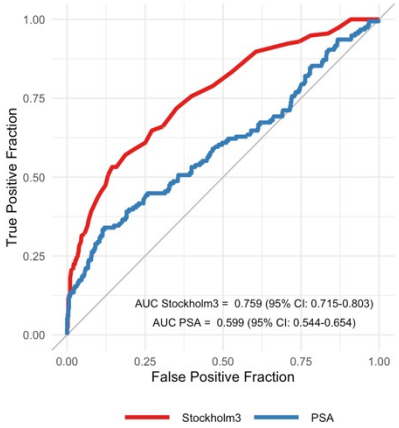
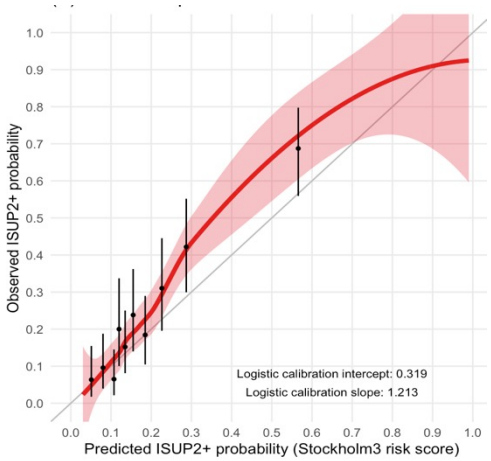
Stockholm3 out-performed PSA and decreased the need of MRI

ROC curves for Stockholm3 and PSA



Calibration plot for Stockholm3



Relative proportion of number of outcomes in the experimental group comparing Stockholm3 with PSA

	Relative proportion	95% CI
MRI	0.64	0.55–0.82
Prostate biopsy	0.92	0.86–1.03
Benign biopsy	0.81	0.66–1.03
Gleason Score 3+3	0.83	0.60–1.13
Gleason Score ≥3+4	1	

Source: Nordström et al Lancet Oncology 2021

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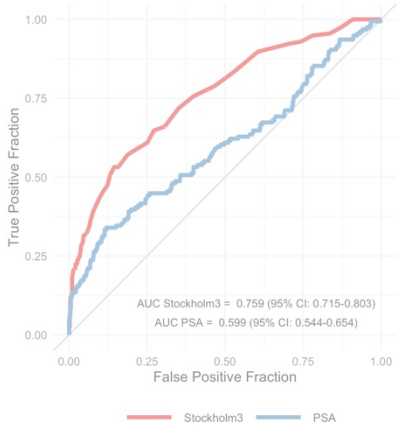
Stockholm3 out-p… the need of MRI

ROC curves for Stockholm3 and PSA



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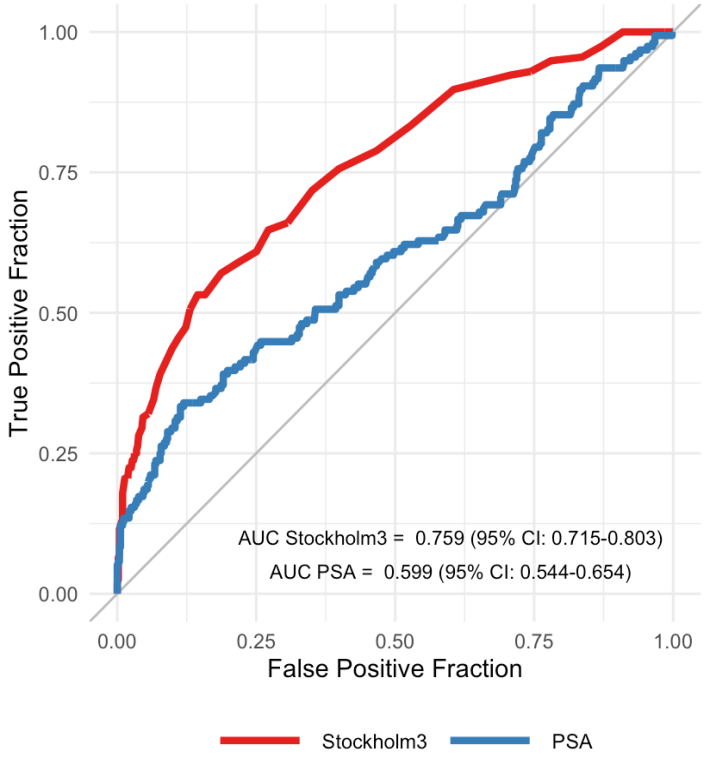

Source: No…

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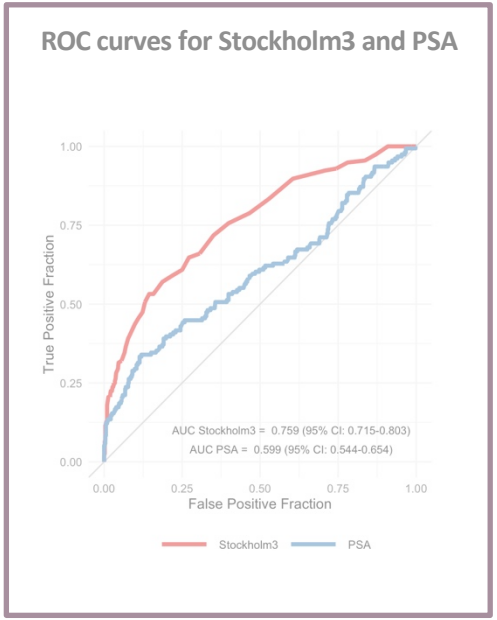
Stockholm3 out-performed

f MRI



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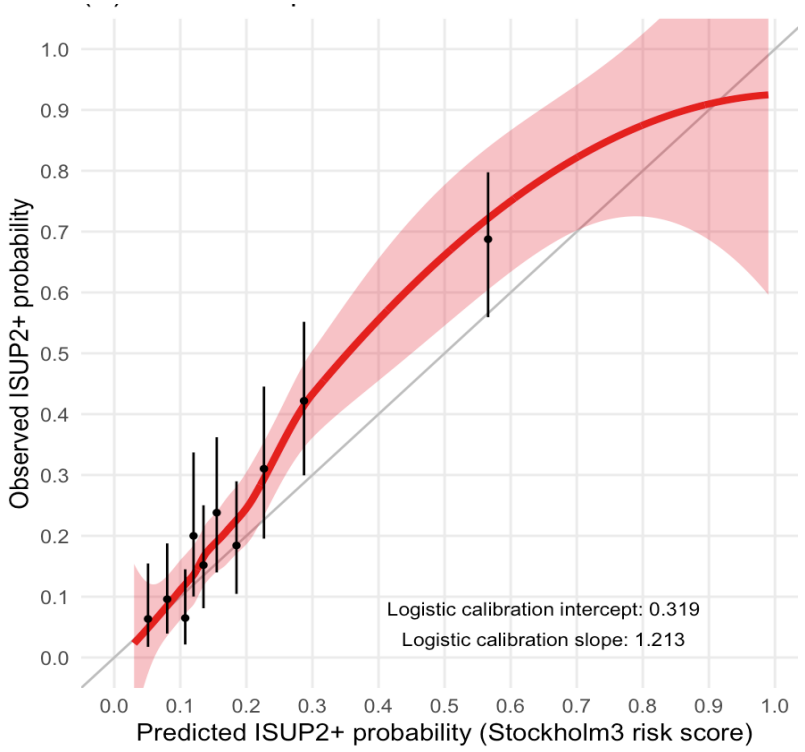

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Source: Nordström et al Lancet O

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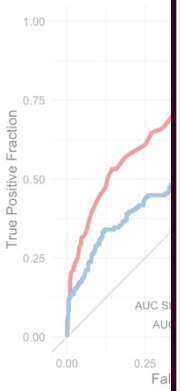
Stockho

ed of MRI

ROC curves for



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Stockholm3 validation studies

Norway	Sweden	Denmark (Prima trial)	Swiss/ German	German (Martini)	European	U.S. (Septa; Multiethnic)
Viste et al J Prim H Care 2020	Bergman et al Läkartidn. 2020	Fredsøe et al Eur Urol Onc 2023	Elyan et al Eur Urol Focus 2023	Abstract EAU 2023	Final analysis ongoing	Accepted for presentation

Is prostate cancer screening health-economically reasonable?

Life-time healthcare perspective, microsimulation model

PSA + MRI

- → Moderate cost per QALY vs no screening ($53,736)
- → Cost-effective versus PSA+standard biopsies

Stockholm3 + MRI

- → Moderate cost per QALY vs no screening (€47,000)
- → Stockholm3 with lowest cost per QALY
  - PSA ≥2ng/ml + Stockholm3≥0.15 + MRI + TBx/SBx
- → 60% less MRI with Stockholm3

Hao et al. Eur Urol 2022, Hao et al. JAMA Onc 2022

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Time to implement prostate cancer screening?

SVENSKA DAGBLADET Nyheter Näringsliv Kultur Ledare

”Bristfällig analys stoppar screening för cancer”

Ett undermåligt vetenskapligt underlag har förhindrat ett välinformerat ställningstagande till allmän screening för prostatacancer. En ny analys av kunskapsläget måste göras så att Socialstyrelsen får ett korrekt faktaunderlag, skriver forskare och läkare verksamma inom prostatacancervården.

Olof Akre
professor och överläkare urologi, chef för prostatacancerflödet, Karol
Universitetssjukhuset

Tobias Nordström
specialistläkare urologi, PhD,

Magnus Annerstedt
specialist urologi och verksa
Urologcentrum, Odenplan

Henrik Grönberg
professor och överläkare, an
Prostatacancercentrum St

Karolinska Institutet

DAGENS Medicin

DEBATT | CANCER

”Alla äldre män bör erbjudas att testa sig för prostatacancer”

Socialstyrelsen har lagt en våt filt över ett av våra största hälsoproblem – att 5 procent av svenska män dör av prostatacancer, skriver debattörerna.

Publicerad: 2018-04-25 07:00 Skriven av: Jonas Hugosson, Sigrid Carlsson, Per-Anders Abrahamsson, Anders Bjartell, Pär Stattin och Peter Wiklund.

Jonas Hugosson, professor i urologi, överläkare och avdelning
Sahlgrenska akademin vid Göteborgs universitet. Sigrid Carls
urologi. Sahlgrenska akademin Göteborg, samt Memorial Slo
York, USA. Per-Anders Abrahamsson, professor i urologi, Lun
New York, f d generalsekreterare för European Association o
och överläkare i urologi, institutionen för translationell medic
universitetssjukhus. Pär Stattin, professor och överläkare i ur
vetenskaper. Akademiska sjukhuset, Uppsala. Peter Wiklund
institutionen för molekylär medicin och kirurgi, sektionen för
i Stockholm.

Socialstyrelsen

Start > Kunskapsstöd och regler > Regler och riktlinjer > Nationella screeningprogram > Slutliga rekommendatione

Prostatacancer – screening med PSA-prov med eller utan annat kompletterande test

DAGENS NYHETER.

E-DN ARKIVET KORSORD KUNDSERVICE DN.VR KUNDERBJUDANDEN

Nyheter Ekonomi Kultur Sthlm Sport ♥ Mitt DN Ledare DN Debatt DN.TV ≡ Mer

Nyheter

Professor: Screening kan halvera dödligheten i prostatacancer

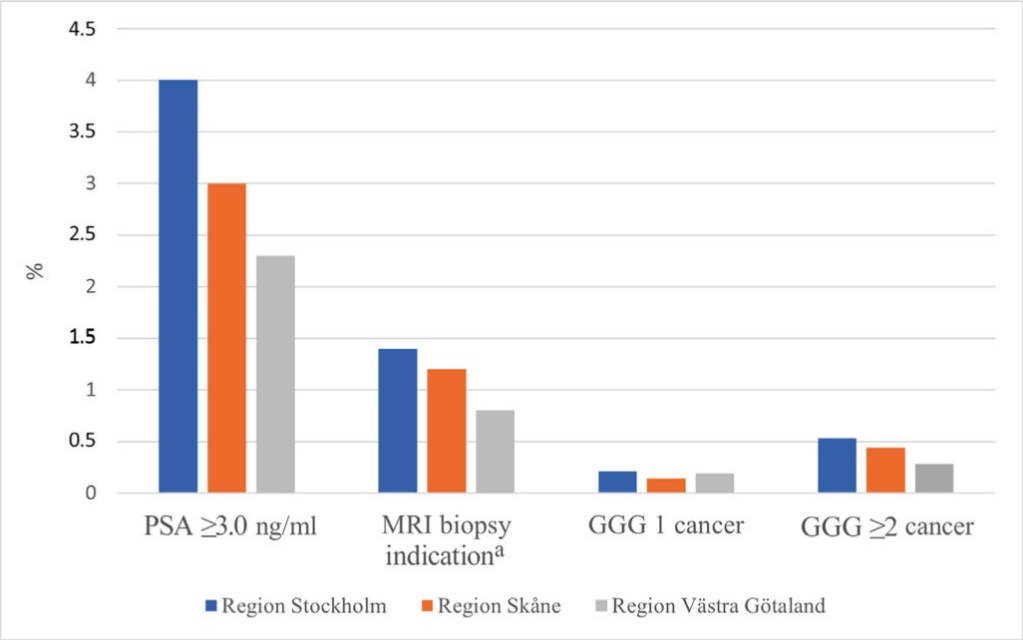
Organised prostate cancer testing has been initiated in Sweden

- Organised invitations with structured information (pro/con)
- Pilot form – supported by national government
- Mainly PSA+MRI+targeted/syst bx
- Parallell scientific evaluations (national register)

- 2020-22 Göteborg, Malmö, Stockholm
- 2023 10 / 24 regions

REGIONALA CANCERCENTRUM I SAMVERKAN

First lessons from OPT:
35% participation rate and variability in proportion positive on PSA and MRI



Among 50 yr participants:

- 35% participation rate
  → n=23,855
- PSA ≥3 ng/ml:
  → 2.3% – 4.0%
- Negative MRI (PI-RADS <2)
  → 54% - 69%
- Cancer detection (ISUP≥2)
  → 0.3-0.5% (n=93)

Bratt et al Eur Urol 2023

Conclusions

- Riskprediction tools shifts benefit/harm-balance of prostate cancer detection
- Screening might be health-economically reasonable
- Governmentally supported organised testing is feasible
- Improved re-screening strategies are needed
- Quality control is essential
- STHLM3MRI 6yr screen performed 2024 including entire study population

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Funding

Cancerfonden

VETENSKAPSRÅDET
THE SWEDISH RESEARCH COUNCIL

FORTE

StratCan
STRATEGISKA FORSKNINGSPROGRAMMET INOM CANCER VID KAROLINSKA INSTITUTET

Stockholms läns landsting

PROSTATACANCER FÖRBUNDET

Key Stockholm publications

Reference	Year	Journal	Size (N)	Focus
Nordström et al	2014	EUROPEAN UROLOGY	531	Comparing two existing blood-tests
Grönberg et al	2015	THE LANCET Oncology	58,818	New test Stockholm3 in screening setting
Eklund et al	2016	EUROPEAN UROLOGY FOCUS	103,970	Stockholm3 in clinical practice
Grönberg et al	2018	EUROPEAN UROLOGY	532	Combining Stockholm3 + MRI in clinical cohort
Nordström et al	2018	Prostate Cancer and Prostatic Diseases	5,291	PSA density in screening cohort
Bergman et al	2018	Läkartidningen	547	Real world experiences in Sweden
Viste et al	2020	Scandinavian Journal of Primary Health Care	4,784	Real world experience in Norway
Nordström et al	2021	THE LANCET Oncology	12,750	Combining Stockholm3 + MRI in screening setting
Eklund et al	2021	The NEW ENGLAND JOURNAL of MEDICINE	12,750	PSA + MRI in screening setting
Hao et al	2022	EUROPEAN UROLOGY	n/a	Cost-effectiveness Stockholm3
Wallden et al	2022	EUROPEAN UROLOGY OPEN SCIENCE	2,511	Stockholm3 + MRI vs Swedish guidelines
Nordström et al	2023		1,500	**Repeated screening** with PSA + MRI, many negative MRIs

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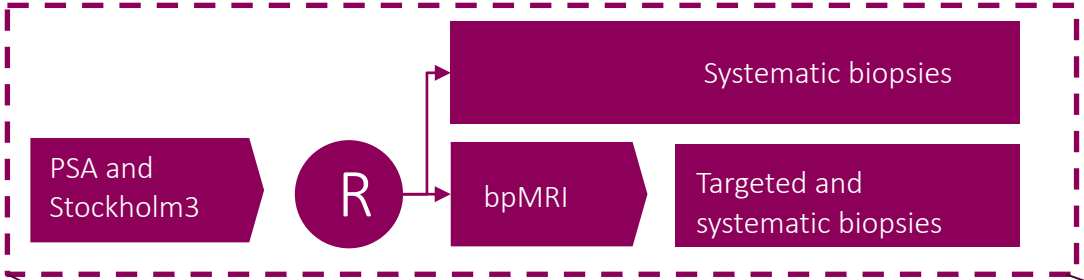
STHLM3 MRI is a screen-by-invitation paired and randomized study



Screen-by-invitation 50-74 yrs (median 61yrs)

12,750 participants (26% participation rate)

Paired step: PSA + Stockholm3 blood-test (clinical, protein, genetic score)

Randomized step, exp arm:

Short protocol bpMRI (15 min)

3-4 BK Medical fusion bx/target + syst bx in men with PI-RADS≥3

Centralized MRI and pathology

High proportion negative MRIs in screening cohorts

	STHLM3MRI	Göteborg-2	OPT Sweden
Median age	61	56	50
Number of MRIs	846	765	645
PI-RADS 1-2	62% (n=521)	64% (n=488)	63% (n=409)
PI-RADS 3	21% (n=175)	8% (n=65)	21% (n=137)
PI-RADS 4	10% (n=85)	20% (n=150)	10% (n=67)
PI-RADS 5	8% (n=65)	7% (n=52)	5% (n=32)

Eklund et al. New Engl J Med 2021, Hugosson et al New Engl J Med 2022, Bratt et al Eur Urol 2023

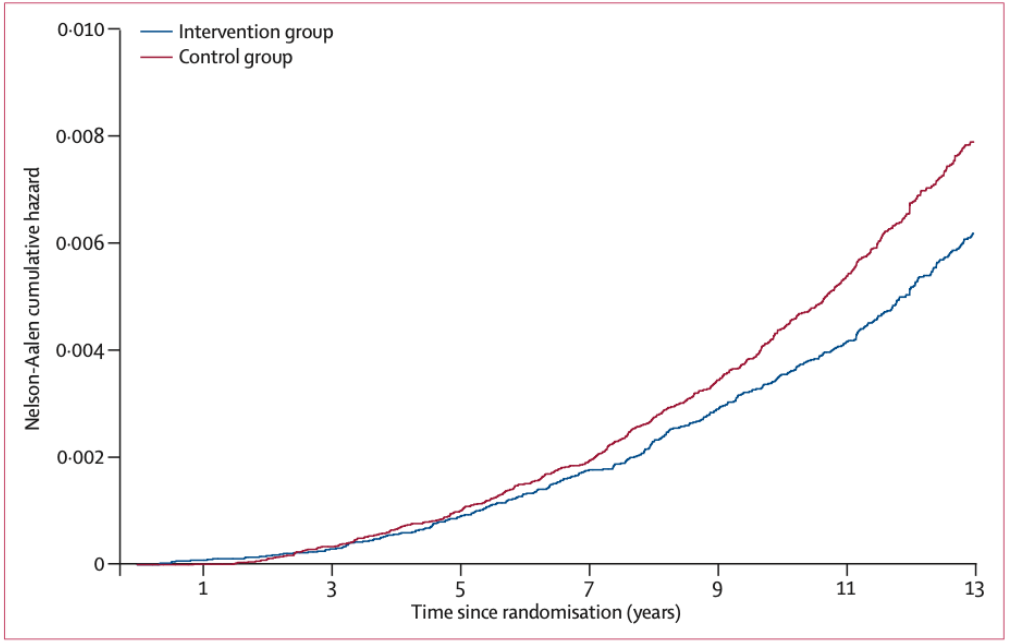


Figure 2: **Nelson–Aalen estimates of cumulative prostate cancer mortality (all centres, excluding France)**

ERSPC 16 years:

≈ 20% ↓ PC-mortality
Number needed to invite 570
Number needed to diagnose 18

Fritz Schröder et al Lancet Onc 2014; Hugosson et al Eur Urol 2019