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Platinum Priority – Prostate Cancer

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Prostate Cancer Diagnostics Using a Combination of the Stockholm3 Blood Test and Multiparametric Magnetic Resonance Imaging

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Abstract

Background: More specific diagnostic for prostate cancer is needed to decrease overdetection and number of diagnostic procedures.
Objective: To assess the performance of combining a blood-based biomarker panel and magnetic resonance imaging (MRI)-targeted biopsies for prostate cancer detection.
Design, setting, and participants: We used a prospective, multicenter, paired diagnostic study design. A total of 532 men aged 45–74 yr referred for prostate cancer workup were included during 2016–2017.
Intervention: Participants underwent blood sampling for analysis of the Stockholm3 test including protein biomarkers, genetic polymorphisms, and clinical variables; 1.5 T MRI; systematic prostate biopsies; and MRI-targeted biopsies to lesions with Prostate Imaging Reporting and Data System version 2 $\geq$3.
Outcome measurements and statistical analysis: The main outcome was numbers of detected prostate cancer characterized by grade group (GG) and the number of performed biopsies using relative sensitivity (RS).
Results and limitations: Median prostate-specific antigen was 6.3 ng/ml, and mean age was 63.9 yr. Targeted and systematic biopsies detected 170 and 162 GG $\geq$2 tumors, respectively (RS 1.05; 95% confidence interval [CI] 0.96–1.14). Compared with performing systematic biopsies on all men, performing targeted and systematic biopsies only on men with >10% risk of GG $\geq$2 cancer, as predicted by the Stockholm3 test, required 62% (95% CI 58–66) of the biopsy procedures and detected 58% (95% CI 48–70) of GG 1 disease, with increased sensitivity for GG $\geq$2 detection (RS 1.10; 95% CI 1.02–1.17). Performing only targeted biopsies in men with elevated Stockholm3 test altered these results only slightly. Compared with performing systematic and targeted biopsies on all men, performing this only for men with an elevated Stockholm3 test decreased detection of GG $\geq$2 cancer slightly (RS 0.92; 95% CI 0.88–0.95). Limitations include lacking knowledge of true disease prevalence.
Conclusions: These findings provide evidence that strategies combining the blood-based Stockholm3 test and MRI-targeted biopsies can be used to inform biopsy decision making.
Patient summary: In this study, 532 men coming for prostate cancer workup underwent blood sampling, and both traditional and magnetic resonance imaging/fusion-guided prostate biopsies. We report that performing targeted biopsies only in men with an elevated risk as assessed by the Stockholm3 test saved biopsies, decreased overdetection, and maintained the number of detected high-grade cancers.

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1. Introduction

Prostate-specific antigen (PSA)-driven identification of men with an increased risk of harboring clinically significant prostate cancer (csPCa) followed by systematic prostate biopsies has been shown to reduce prostate cancer mortality [1,2]. However, both PSA and the traditional use of systematic biopsies (SBx) guided by transrectal ultrasound (TRUS) have demonstrated poor sensitivity and specificity [3,4]. This leads to high rates of overdiagnosis and overtreatment [1,5], but also to misrepresentations of correct tumor grading, illustrated by the high rates of disease reclassification at radical prostatectomy [6]. Thus, both diagnostic and treatment decisions are often based on information that is not representative of the severity of disease.

Prediction models based on blood tests, such as Prostate Health Index (PHI), 4KScore, and Stockholm3 (STHLM3) test, or risk calculators based on, for example, the European Randomised Study of Screening for Prostate Cancer (ERSPC) trial data have been suggested to improve risk stratification for identifying men with prostate cancer [7–11]. The STHLM3 test includes information on clinical parameters, protein levels, and a genetic score, and has been shown to decrease overdiagnosis and number of performed prostate biopsies with maintained sensitivity for clinically relevant prostate cancer [10,12].

Magnetic resonance imaging (MRI) has emerged as an alternative to improve identification of prostatic lesions, showing high sensitivity to detect clinically significant disease [3]. There is also evidence that MRI tends to decrease detection of low-risk disease and spare men without MRI lesions from biopsy [13]. Thus, MRI followed by targeted biopsies (TBx) has been suggested, and multiple studies have shown slightly better detection of significant cancer and decreased detection of insignificant cancer as compared with SBx [14–16].

We investigated whether the combination of the blood test STHLM3 and MRI-TBx can improve diagnosis in terms of reducing the number of biopsied men and grade group (GG) 1 tumors while maintaining the sensitivity to find men with GG ≥2 prostate cancer [17].

2. Patients and methods

2.1. Study design

The STHLM3 MRI study was a prospective, multicenter, paired diagnostic study registered as NCT02788825 (ClinicalTrials.gov). Patients were recruited from 2016-05-12 and during 12 mo from three sites—Stockholm (Sweden), and Oslo and Tønsberg (Norway). Men aged 45–75 yr referred to any of the sites for prostate cancer diagnostic workup (prostate biopsies or prebiopsy MRI) were eligible for inclusion, and participants underwent blood sampling, MRI, and a combined biopsy procedure. The study sites were characterized by high experience of MRI/fusion biopsies in Oslo (>1000 procedures) and Tønsberg (>1000 procedures), and low experience in Stockholm where MRI/fusion was in use 4 mo prior to the start of the study.

We compared the performance of MRI-TRUS fusion TBx and/or SBx, with and without the requirement of a prior positive STHLM3 test (Fig. 1).

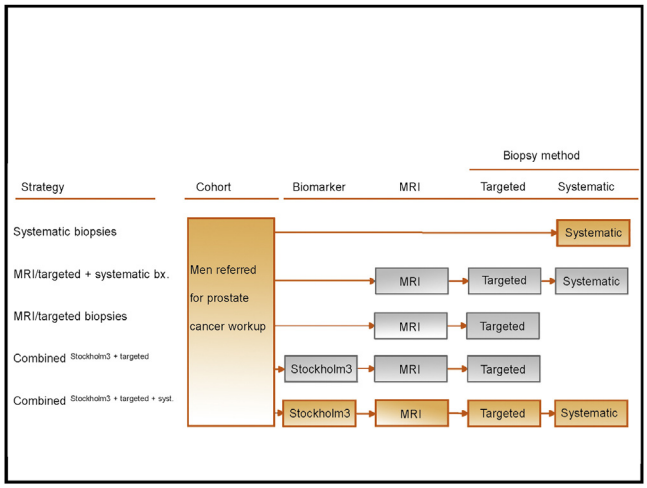

Fig. 1 – Diagnostic strategies for the detection of prostate cancer assessed in STHLM3 MRI. bx. = biopsy; MRI = magnetic resonance imaging; STHLM3 = Stockholm3.

The main endpoint was defined as cancer detection using either systematic or targeted prostate biopsies (ie, a man was considered to have a GG ≥2 cancer if it was detected using either SBx or TBx). The predefined STHLM3 blood test includes age, free and total PSA, hK2, MSMB, MIC1, DRE, a polygenic risk score, HOXB13 SNP, and prostate volume (measured by MRI in this study). The test gives the percentage risk of GG ≥2 cancer [10].

As a priori specified, men with incomplete data on MRI or SBx were excluded from the analysis. Men with incomplete STHLM3 data (n = 51) were also excluded. This was mainly from Norwegian participants and due to aliquot degradation caused by prolonged transportation.

The primary definition of csPCa was GG ≥2; analyses using alternative definitions of csPCa were performed and are presented in Table 1. All participants provided written consent. The regional ethics committees in Stockholm and Oslo approved the study (2016/392-31 and 2016/684).

2.2. Procedures

2.2.1. Magnetic resonance imaging

MRI was performed using a standardized detection protocol (Supplementary Table 1) compliant with European Society of Radiology Guidelines, except that dynamic contrast enhancement was omitted in order to decrease protocol complexity and acquisition time. We used 1.5 T magnetic field without endorectal coil. T1- and T2-weighted images; diffusion-weighted images; b-values of 100, 450, and 800 with calculated apparent diffusion coefficient map (ADC); and separately a b1500 were acquired. Participants were instructed to refrain from sexual activity 3 d prior to MRI. A minimal enema (Microlax) was administered a few hours prior to the examination, and intramuscular glucagon (1 mg) or Buscopan was given just before the examination. The time of acquisition was 16 min for the MRI sequences per participant.

MRI scans were reported according to the Prostate Imaging Reporting and Data System version 2 (PI-RADS v2), where up to three lesions with PI-RADS grade ≥3 were marked for TBx and defined MRI lesions in this study [18]. Thirty participants without any PI-RADS ≥3 lesion had diffuse changes on the MRI and were counted as needing SBx. One or two experienced uroradiologists per site reviewed all MRI series. MRI reading variability was assessed using multivariable regression, and blinded cross validation was performed for a small series (Supplementary material).

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Table 1 – Comparisons between MRI/targeted biopsies and systematic prostate biopsies using different definitions of significant prostate cancer

	Cancers detected in 532 men by biopsy strategy				
	Systematic biopsies	MRI/targeted and systematic biopsies		MRI/targeted biopsies only	
Grade group	*n*	*n*	Relative sensitivity vs systematic bx. (95% CI)	*n*	Relative sensitivity vs systematic bx. (95% CI)
GG 1 (Gleason score 6)	101	97	0.96 (0.86–1.07)	83	0.82 (0.69–0.98)
GG ≥2 (Gleason score ≥7)	162	194	1.20 (1.13–1.28)	170	1.05 (0.96–1.15)
GG 3 (Gleason score ≥4 + 3)	35	45	1.29 (1.04–1.63)	41	1.17 (0.88–1.56)
GG ≥4 (Gleason score ≥8)	21	30	1.43 (1.14–1.90)	25	1.19 (0.83–1.75)
GG ≥2 or cancer ≥4 mm	218	246	1.13 (1.05–1.21)	228	1.05 (0.96–1.14)
GG ≥3 or cancer ≥6 mm	187	205	1.10 (1.00–1.21)	198	1.06 (0.95–1.18)

bx. = biopsy; CI = confidence interval; GG = grade group; MRI = magnetic resonance imaging.
Cancers were detected in 532 men coming for prostate cancer workup.
Relative sensitivity was calculated as the number of cancers detected by the investigated strategy (ie, MRI/targeted and systematic biopsies) divided by the number of cancers using the comparator (ie, systematic biopsies).

2.2.2. Blood analysis

Blood sampling was performed after inclusion and before the biopsy procedure. EDTA tubes (2 × 4 ml) and a lithium heparin tube (1 × 4 ml) were collected. One of the EDTA tubes and the lithium heparin tube were centrifuged for 10 min in 2000 *g* before plasma was decanted. All tubes were frozen at −20 °C and transported to KI Biobank, Karolinska Institutet, before analysis at Karolinska University Laboratory, Stockholm. The STHLM3 test analyses were blinded to urologists and pathologists. The STHLM3 test is clinically available as a laboratory-developed test, currently priced at €250–300.

2.2.3. Prostate biopsies

All participants underwent a combined biopsy procedure with two to three TBx to each marked lesion using MRI/fusion, after which 10–12 systematic prostate biopsies were performed by the same urologist. To minimize image quality problems due to postbiopsy bleeding, TBx were performed prior to SBx.

Targeted biopsies were undertaken using the Koelis system (Koelis Inc., Oslo, Norway), Artemis system (Eigen Inc., Tønsberg, Norway), and BioJet system (D&K Technologies GmbH, Stockholm, Sweden).

Each needle biopsy core was formalin fixed in a separate container and graded according to the International Society of Urological Pathology 2014 modification [19].

Pathological specimen was locally reviewed by experienced uropathologists (SiV Tønsberg, Unilabs Stockholm, Oslo University Hospital).

2.3. Statistical methods

The STHLM3 scores were computed using the model based on data from the STHLM3 diagnostic study involving 59 000 men [10]. As a priori defined, an STHLM3 test >10% risk of GG ≥2 was considered positive.

Relative sensitivity (RS) was computed as the sensitivity to detect cancer using one diagnostic strategy relative to the sensitivity of the reference strategy. Subgroup analysis on main endpoint was performed for men by study site (Supplementary Tables 2 and 3).

Confidence intervals (CIs) are two-sided 95% empirical bootstrap intervals based on 1000 bootstrap samples. Sensitivity analyses using the STHLM3score for imputation of missing biopsy data did not alter results materially (Supplementary Table 4). The analyses were performed using the R statistical software version 3.2.5.

2.4. Sample size

The prospective power calculation for this study was based on previously reported prevalence of GG ≥2 in SBx [10], 60–80% men with PI-RADS ≥3 findings on MRI, and effect estimates indicating increased detection of intermediate/high-risk cancer in TBx versus SBx (40% vs 35%) [15]. All calculations were based on 80% power and 5% significance (two sided), generating a minimum size of complete data on 500 participants. Inclusion was stopped when this was reached. The final dataset included participants with finalized data also after this point.

3. Results

A total of 532 participants had STHLM3 test data, and underwent MRI and prostate biopsy. Participant demographics are shown in Table 2. Median PSA was 6.3 ng/ml (interquartile range [IQR] 4.4 ng/ml), and median STHLM3 risk was 17% (IQR 6–36%). Of all participants, 389 (73%) had no previous prostate biopsy. A total of 204 (38%) men had ≤10% risk of GG ≥2 prostate cancer as assessed by the STHLM3 test.

3.1. MRI results

Nineteen percent (103/532) of the full cohort and 11% (35/327; $p < 0.01$) of men with positive STHLM3 test (>10%) had no reported PI-RADS ≥3 lesion on MRI and had thus no TBx. Men with a positive STHLM3 test had larger primary lesions (ie, lesions with the highest PI-RADS score), compared with men with a negative STHLM3 test (nonparametric comparison of mean lesion volume: 2.5 vs 0.9 cc, $p < 0.05$).

3.2. Comparison between TBx and SBx

In 532 men, MRI/TBx detected 170 GG ≥2 cancers and SBx detected 162 (RS 1.05; 95% CI 0.96–1.14). TBx combined with SBx detected 194 GG ≥2 cancers (Fig. 2 and Table 1). Detection rates for alternative significant cancer definitions are shown in Table 1. TBx detected 83 GG 1 cancers and SBx detected 101 (RS 0.82; 95% CI 0.69–0.96). Compared with performing only SBx, the strategy of performing only TBx saved 13% of biopsies (95% CI 10–16).

One of 35 and three of 33 men with GG 3 and ≥4 on SBx had benign or GG 1 findings on TBx. For these four men, PI-RADS scores were 3 ($n = 1$), 4 ($n = 2$), and 5 ($n = 1$).

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Table 2 – Characteristics of participants in STHLM3 MRI

	Stockholm	Oslo	Tønsberg
Participants, *n*	160	236	136
Age (yr), mean (SD)	63 (6.2)	65 (7.8)	64 (6.8)
PSA (ng/ml), median (IQR)	6.2 (4.8–8.2)	6.0 (4.0–9.0)	7.1 (4.7–11)
Stockholm3 [a] (%), median (IQR)	8.0 (4–20)	22 (9–48)	20 (7–49)
Prostate volume (cc), median (IQR)	51 (38–70)	42 (32–54)	44 (33–55)
Previous prostate biopsy (%)	49	23	8.1
PI-RADS, *n* (%)			
≤2	65 (40)	2 (1)	36 (26)
3	65 (41)	98 (41)	32 (24)
4	18 (11)	66 (28)	37 (27)
5	12 (8)	70 (30)	31 (23)
No. of lesions on MRI, mean (SD)	0.8 (0.7)	1.7 (0.8)	0.9 (0.7)
Grade group, *n* (%)			
1 (Gleason score 6)	18 (11)	55 (23)	24 (18)
2 (Gleason score 3 + 4)	20 (12)	63 (27)	20 (15)
3 (Gleason score 4 + 3)	9 (6)	25 (11)	11 (8)
≥4 (Gleason score ≥4 + 4)	4 (3)	20 (9)	22 (16)

IQR = interquartile range; MRI = magnetic resonance imaging; PI-RADS = Prostate Imaging Reporting and Data System version 2; PSA = prostate-specific antigen; SD = standard deviation; STHLM3 = Stockholm3 test.
[a] The Stockholm3 test gives the percentage risk of Gleason score ≥7 cancer.

Of men with benign findings or GG 1 cancers on SBx, 10.4% (*n* = 32/308) had higher-grade cancer findings on TBx (GG 2 [*n* = 20], GG 3 [*n* = 6], GG ≥4 [*n* = 6]).

3.3. *Comparisons between different strategies to select men for prostate biopsy*

Fig. 1 and Table 3 show strategies for cancer detection. Performing SBx only in men with a positive STHLM3 test has been described before [10]. Compared with performing SBx in all men, this strategy showed acceptable sensitivity in detecting GG ≥2 cancer to when performing SBx in all men (RS 0.94; 95% CI 0.90–0.97), decreased detection of GG 1 tumors by 30% (95% CI 21–39), and saved 38% (95% CI 34–43) of the biopsies being performed.

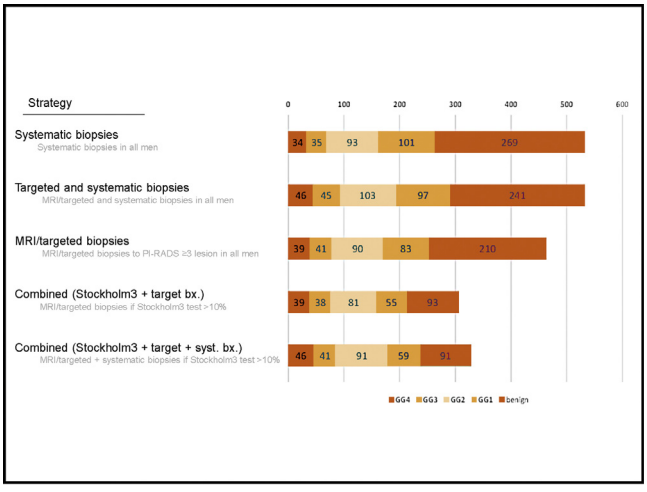

Fig. 2 – Number of detected prostate cancers and performed biopsies by diagnostic strategy in 532 men coming for prostate cancer workup in clinical practice. bx. = biopsy; GG = ISUP Grade Group; MRI = magnetic resonance imaging; PI-RADS = Prostate Imaging Reporting and Data System.

Compared with SBx in all men, performing both MRI/TBx and SBx, but only in men with elevated STHLM3, increased detection of GG ≥2 tumors by 10% (*n* = 178 vs 162; 95% CI 1.03–1.18), detecting 58% (95% CI 0.48–0.68) of GG 1 tumors, and would spare 38% of performed biopsy procedures (Table 3). This strategy of selecting men for combined MRI/TBx and SBx using the STHLM3 test was associated with slightly lower detection of GG ≥2 cancer (RS 0.92; 95% CI 0.88–0.95) when comparing with performing both MRI/TBx and SBx in all men.

The combined strategy of performing only MRI/TBx for men with positive STHLM3 test showed similar sensitivity to detect GG ≥2 prostate cancer compared with the SBx (RS 0.98, 95% CI 0.89–1.07), but decreased detection of GG 1 tumors by 46% (95% CI 33–56) and saved 42% (95% CI 38–47) of prostate biopsies (Table 3).

Sensitivity analysis excluding the 27% men with previous prostate biopsy did not affect results materially. The negative predictive value using any GG ≥2 cancer on TBx or SBx as an endpoint was 92% for STHLM3 test (negative: ≤10%), 93% for MRI (negative: PI-RADS ≤2), and 99% if both tests were negative.

4. Discussion

We have performed a prospective, clinical study using a paired design to assess the effect of using biomarkers and MRI-based TBx for prostate cancer detection in men coming for prostate workup at three different centers in Sweden and Norway. Using the locally available MRI/fusion systems, we found that current practice without prebiopsy MRI is outperformed by both a biomarker-based strategy alone, and by TBx strategies with or without improved risk stratification using the STHLM3 test. Using a combined strategy with the STHLM3 blood test and MRI TBx, detection of GG 1 tumors and the number of biopsies needed were almost halved, without decreased sensitivity to detect GG ≥2 cancer, as compared with using SBx.

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Table 3 – Comparisons between diagnostic strategies in 532 men coming for prostate cancer workup in clinical practice

Strategy		Performed biopsies		Cancer detection			
				Grade group ≥2 (Gleason score≥7)		Grade group 1 (Gleason score 6)	
		n	% (95% CI)	*n*	Relative sensitivity (95% CI)	*n*	Relative sensitivity (95% CI)
MRI/targeted biopsies	Vs systematic bx. Vs MRI/targeted + systematic bx.	463/532	87 (84, 90) 170/194	170/162	1.05 (0.95, 1.14) 0.88 (0.83, 0.92)	83/101 83/97	0.82 (0.69, 0.97) 0.86 (0.75, 0.97)
Combined (Stockholm3 + MRI/target)	Vs systematic bx. Vs MRI/targeted + systematic bx.	306/532	58 (53, 62)	158/162 158/194	0.98 (0.88, 1.07) 0.81 (0.76, 0.87	55/101 55/97	0.54 (0.43, 0.66) 0.57 (0.45, 0.69)
Combined (Stockholm3 + MRI/target + syst.)	Vs systematic bx. Vs MRI/targeted + systematic bx.	328/532	62 (58, 66)	178/162 178/194	1.10 (1.02, 1.17) 0.92 (0.88, 0.95)	59/101 59/97	0.58 (0.48, 0.70) 0.61 (0.50, 0.71)

bx. = biopsy; CI = confidence interval; MRI = magnetic resonance imaging.
Relative sensitivity was calculated as the number of cancers detected by the investigated strategy (ie, one MRI/targeted) divided by the number of cancers using the comparator (ie, systematic biopsies in all). Systematic bx.—performing systematic biopsies in all men; MRI/targeted + systematic bx.—performing targeted and systematic biopsies in all men; MRI/targeted biopsies—performing MRI/targeted biopsies on all men; Combined Stockholm3 + MRI/target bx.—performing MRI/targeted biopsies only in S3M-positive men; Combined Stockholm3 + MRI/target + syst. bx.—performing MRI/targeted and systematic biopsies only in S3M-positive men.

4.1. TBx for prostate cancer detection

Performing only TBx in all men with visible lesions on MRI in this cohort shows slightly higher sensitivity to detect csPCa and decreased detection of GG 1 tumors, and saves approximately every fifth prostate biopsy procedure compared with using SBx on all men.

The recent PROMIS study recently showed 93% sensitivity of MRI to detect clinically significant cancer using template saturation biopsies as reference standard [3]. Several other studies have shown that the strategy of targeting biopsies to MRI lesions have a slightly higher rate of detection of significant prostate cancer and a lower rate of detection of insignificant prostate cancer compared with SBx [14–16]. Together with previous evidence, our findings support the introduction of prebiopsy MRI scans in routine care.

The effect on decreasing biopsy numbers and overdiagnosis would be most pronounced if men without lesions on MRI were recommended not to undergo biopsy. The size of this proportion of men is highly dependent on cancer prevalence and the type of cohort, ranging from the relatively low 19% in this current practice cohort to approximately 50% in a screening setting [20]. The negative predictive value of MRI is also dependent on the disease prevalence [21]. From a health economical point of view, the extra costs associated with MRI scans have been shown to be compensated for by reducing treatment costs resulting from fewer diagnoses of insignificant cancer and better estimation of tumor aggressiveness. However, this balance also depends on disease prevalence, highlighting the importance of patient selection [22]. However, the health economic impact of combining STHLM3 and MRI is unknown and will be subject to further studies. Finally, a learning curve when introducing targeted prostate biopsies is expected [23]. This is supported by the finding that the lower experienced Stockholm site in our study showed lower sensitivity to detect GG ≥2 cancer than the Norwegian sites (Supplementary Table 2).

4.2. STHLM3 test for prostate cancer detection

Corroborating previous studies [10,13], we show that a biomarker-based strategy where only men with an increased STHLM3 score undergo SBx saves biopsies, decreases GG 1 detection, and maintains GG ≥2 detection.

The insufficient predictive value of PSA for prostate cancer detection is well known and several other risk prediction tools, including both traditional risk calculators such as the ERSPC risk calculator and blood-based tests such as the PHI and 4KScore, have also been suggested to aid in making decisions regarding who would be recommended for prostate biopsies [7–11]. The fact that as many as 31% of the biopsy-naïve participants in this multisite and contemporary clinical cohort had <10% risk of GG ≥2 prostate cancer, as predicted by the STHLM3 test, illustrates the need for improved selection of men for prostate cancer workup.

4.3. Assessment of combining biomarkers and MRI for prostate cancer detection

Previous publications show that the kallikrein-based PHI test used with or without the prostate volume (PHI density) might add information to MRI findings in the detection of prostate cancer [24–26]. Further, Fenstermaker and colleagues [27] showed that the levels of the urine-based PCA3 are associated with MRI findings and cancer detection using TBx. We assessed a combined strategy where only men with an elevated prostate cancer risk, as assessed by STHLM3 test, undergo MRI and subsequent TBx of suspicious lesions with or without the addition of SBx. We report that the combined strategy when omitting SBx might decrease overdetection dramatically, decreasing GG 1 tumors by 46% and saving 42% of the biopsies without affecting the

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sensitivity to detect significant cancer, as compared with using SBx in clinical practice. The alternate strategy of performing both SBx and TBx only in men with an elevated STHLM3 test score detected somewhat more GG ≥2 cancers, to the cost of slightly more GG 1 tumors and number of performed biopsies. Combining the STHLM3 test with TBx with or without the addition of SBx outperforms both the STHLM3 test and the TBx alone.

There are limitations to this study. External validations of the STHLM3 test in non-Scandinavian populations are currently being performed. Although it has previously been shown that TBx decrease disease misclassification [14], in the absence of prostatectomy specimen the true disease prevalence is unknown. This pragmatic study performed in clinical practice includes data from several clinical departments (urology/radiology/pathology/Biobank/laboratory) in a complex logistic chain. Although quality of data has been monitored continuously, some final data are missing. For biomarker data, a few samples were of insufficient quality for analysis due to long transport time between Norway and Sweden. Men underwent biopsies according to the local clinical praxis at each site, that is, all men underwent SBx in Stockholm and Tønsberg, whereas men in Oslo without lesions on MRI did not undergo biopsies. Therefore, we report the site-specific numbers in Supplementary tables. Further, we performed sensitivity analyses imputing missing biopsy and biomarker data as described in methods. This had a very marginal effect on the results, indicating some robustness of our findings.

5. Conclusions

Many men with a low risk of GG ≥2 prostate cancer are referred for prostate cancer workup. A state-of-the-art risk prediction model can markedly decrease the number of men in this group to save biopsies and reduce diagnosis of low-grade prostate cancer as compared with performing SBx on all men. We report that in men coming for prostate cancer workup, risk stratification with STHLM3 in combination with MRI and TBx with or without the addition of SBx might approximately half the numbers of GG 1 tumors and prostate biopsies without decreasing the sensitivity to detect GG ≥2 cancer.

Author contributions: Tobias Nordström had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Nordström, Grönberg, Eklund, Carlsson, Jäderling.
Acquisition of data: Nordström, Picker, Aly, Jäderling, Landquist, Haug, Carlsson.
Analysis and interpretation of data: Grönberg, Nordström, Ström, Eklund.
Drafting of the manuscript: Grönberg, Nordström, Eklund.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Ström, Eklund.
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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.06.022

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