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Prostate Cancer

# The Stockholm-3 Model for Prostate Cancer Detection: Algorithm Update, Biomarker Contribution, and Reflex Test Potential

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**Abstract**

***Background:*** It has been shown that the Stockholm-3 model (S3M) outperforms prostate-specific antigen (PSA) as a screening tool for prostate cancer.
***Objective:*** To update the S3M, to give a detailed account of the value of each predictor in the S3M, and to evaluate the S3M as a reflex test for men with PSA ≥3 ng/ml.
***Design, setting, and participants:*** During 2012–2015, the Stockholm-3 study evaluated the S3M relative to PSA as tests for Gleason score ≥7 prostate cancers among men aged 50–69 yr. The participants ($n$ = 59 159) underwent both tests, and biopsy was recommended if at least one was positive. A total of 5073 men had a biopsy because of elevated PSA (≥3 ng/ml).
***Outcome measurements and statistical analysis:*** Logistic regression was used to update the S3M: intact PSA was removed, *HOXB13* was included, and the model was fitted to data from the Stockholm-3 training and validation cohorts. To compare S3M with PSA, we fixed the sensitivity for detection of high-grade cancer and evaluated the performance as the number of biopsies needed to achieve that sensitivity for each test.
***Results and limitations:*** The updated S3M slightly improved the area under the receiver operating characteristic curve compared to previously published results (0.75 vs 0.74). When used as a reflex test for men with PSA ≥3 ng/ml, S3M reduced the number of biopsies needed by 34% compared to the use of PSA alone, with equal sensitivity. A limitation is the ethnically homogeneous population.
***Conclusions:*** A major problem with PSA screening—too many unnecessary biopsies—can be mitigated if S3M is used as a reflex test.
***Patient summary:*** To find aggressive prostate cancer with the minimum number of negative biopsies and detection of clinically insignificant cancers, we evaluated the use of a personalized diagnostic prediction model as a second test for men with a positive prostate-specific antigen (PSA) test. We found that this two-step approach could reduce prostate biopsies by a third compared to using PSA alone.


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## 1. Introduction

Although prostate-specific antigen (PSA) measurement is suitable for prostate cancer screening because of its low cost and noninvasive nature, it has low specificity at acceptable sensitivity levels. This is because nonmalignant conditions such as inflammations and benign prostate hyperplasia may cause increases in PSA levels, and prostate cancer can exist without an increase in PSA. The low specificity leads to frequent prostate biopsies in men with benign conditions,

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and to overdiagnosis of indolent prostate cancer. Use of PSA for disease screening is therefore controversial [1]. One way to improve the specificity of prostate cancer screening is to use a second test—a reflex test—for men with increased PSA levels [2]. The reflex test needs to be more predictive of cancer than PSA alone, and since only men with a higher risk of prostate cancer undergo the test, a higher cost may be justified. There are several possible tests for this purpose, such as percentage free PSA, the 4K score [3], the Prostate Health Index (PHI) [4], PCA3 [5], and RC3 [6].

In 2015, Grönberg et al [7] published results for the Stockholm-3 (STHLM3) study, in which the individualized prediction model S3M was compared to PSA ≥3 ng/ml as a screening test for prostate cancer. The study was designed so that both tests would detect the same number of Gleason score (GS) ≥7 cancers, and the tests were evaluated in terms of the number of biopsies needed to achieve this. With maintained sensitivity for detecting GS ≥7 disease, use of S3M saved 32% of prostate biopsies compared to screening using PSA ≥3 ng/ml as an indication for a prostate biopsy.

Knowledge of the contributions of separate components in suggested tests is important to understand the performance of the underlying biomarkers and was not presented in detail by Grönberg et al [8]. Furthermore, it is not clear how the S3M will perform in a reflex test setting. Here, we describe an update of the S3M test and analyze the predictive contribution of the biomarkers included in the S3M. We also assess the usefulness of the S3M in a reflex setting whereby the test is used only for subjects with elevated PSA.

## 2. Patients and methods

### 2.1. Participants and study design

The STHLM3 study was a prospective and population-based diagnostic trial designed to compare S3M with PSA ≥3 ng/ml as indications for prostate biopsy [7]. It consisted of a training ($n$ = 11 130) and a validation cohort ($n$ = 47 688), both of randomly invited (no overlap) men aged 50–69 yr and without a previous prostate cancer diagnosis, from Stockholm County, Sweden (Table 1). Data for the training cohort were used to fit the S3M, which was subsequently evaluated in the validation study. STHLM3 used a paired screen-positive design in which the S3M test was analyzed for all participants with PSA ≥1 ng/ml [9]. Each participant was then recommended prostate biopsy if he had PSA ≥3 ng/ml or a S3M probability of GS ≥7 prostate cancer above a fixed threshold. The S3M threshold was set such that both tests (PSA and S3M) detected the same number of GS ≥7 cancers. The indication for biopsy referral was blinded to the study participants, the urologists, and the pathologist. The biopsy procedure followed a standardized protocol using 10–12-core systematic biopsies, with 12 cores if the prostate volume was >35 $cm^3$.

Since the sensitivity for detecting GS ≥7 cancer was the same for both tests by design, the evaluation of the usefulness of the tests could be based on the number of biopsies needed for each test (ie, the number of participants with S3M above the adjusted threshold compared to the number of participants with PSA ≥3 ng/ml), and specifically, how many of these biopsies were cancer-free and cancers graded as GS 6.

In this study, we included all biopsied participants from the pilot study and the validation study, and 331 (of whom 34 underwent biopsy) additional participants who had not had a blood test before the database of the STHLM3 study was locked (total $n$ = 59 149). We excluded men with PSA ≥10 ng/ml ($n$ = 630) and men taking α-reductase inhibitor medication at inclusion ($n$ = 1385; Table 1).

**Table 1 – Characteristics of the study cohort (pilot and validation cohorts for the Stockholm-3 study)**

| | Patients, $n$ (%) | |
|---|---|---|
| | All participants ($n$ = 59 149) | Biopsied participants [a] ($n$ = 7417) |
| Age [b] | | |
| <49 yr | 1791 (3) | 45 (1) |
| 50–54 yr | 12923 (22) | 640 (9) |
| 55–59 yr | 13570 (23) | 1222 (16) |
| 60–64 yr | 14072 (24) | 2031 (27) |
| 65–69 yr | 15998 (27) | 3299 (44) |
| ≥70 | 795 (1) | 180 (2) |
| First-degree relative with prostate cancer | | |
| Yes | 7262 (12) | 1118 (15) |
| No | 51887 (88) | 6299 (85) |
| Previous negative biopsy | | |
| Yes | 1976 (3) | 505 (7) |
| No | 57173 (97) | 6912 (93) |
| Prostate-specific antigen | | |
| <1 ng/ml | 26159 (44) | 2 (0) |
| 1–3 ng/ml | 25350 (43) | 1938 (26) |
| 3–5 ng/ml | 4655 (8) | 3461 (47) |
| 5–10 ng/ml | 2355 (4) | 1613 (22) |
| ≥10 ng/ml | 630 (1) | 403 (5) |
| Medication (5α-reductase inhibitor) | | |
| Yes | 1385 (2) | 180 (2) |
| No | 57764 (98) | 7237 (98) |
| Digital rectal examination | | |
| Abnormal | – | 681 (9) |
| Normal | – | 6736 (91) |
| Prostate volume [c] | | |
| <35 ml | – | 2705 (36) |
| 35–50 ml | – | 2497 (34) |
| ≥50 ml | – | 2215 (30) |
| Biopsy result | | |
| Benign | – | 4618 (62) |
| Gleason 3 + 3 | – | 1558 (21) |
| Gleason 3 + 4 | – | 759 (10) |
| Gleason 4 + 3 | – | 253 (3) |
| Gleason ≥ 4 + 4 | – | 229 (3) |

[a] Participants were recommended a biopsy on a double–blind basis if they were positive for prostate-specific antigen ≥3 ng/ml or the Stockholm-3 model test.
[b] The validation study only included men aged 50–69 yr.
[c] Measured via transrectal ultrasound.

### 2.2. Predictors in S3M

The predictors in S3M include clinical variables (age, first-degree family history of prostate cancer, and a previous biopsy), blood biomarkers (total PSA, free PSA, ratio of free/total PSA, hK2, MIC1, and MSMB), genetic markers (a genetic score based on 254 single-nucleotide polymorphisms [SNPs] and an explicit variable for the *HOXB13* SNP), and prostate examination (digital rectal examination [DRE], and prostate volume). Details of the genetic score have been described by Grönberg et al [7]. The original version of S3M also included intact PSA, but because of interference between the kallikreins in the immunosorbent allergen chip assay it has been removed from S3M. In addition, a new biomarker is included, the *HOXB13* SNP, a rare germline mutation of the *HOXB13* gene with a large effect on the risk of prostate cancer [10]. It is present in 1.3% of healthy Swedish men and is 3.5-fold more common among prostate cancer patients with otherwise similar characteristics. All continuous predictors are included as linear effects and the others (family history,

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