

Molecular Diagnostic Tests for Men at Higher Probability for Prostate Cancer

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Summary and conclusions

SBU's appraisal of the evidence

Many men, on their own initiative, are tested for the concentration of prostate specific antigen (PSA) in their blood. A high PSA concentration suggests an increased probability of cancer. Men at higher probability often receive further examination by prostate biopsy, an invasive procedure. Since prostate biopsy can lead to complications, unnecessary procedures should be avoided. A result of slightly to moderately raised PSA concentration is difficult to interpret, and uncertainty concerning the necessity of biopsy is common. To avoid unnecessary biopsies, clinicians need new, complementary tests to better determine which men with slightly to moderately raised PSA concentration actually require further investigation.

This report assesses the diagnostic accuracy of three new molecular urine tests (uPCA3, TMPRSS2:ERG, and me-GSTP1) when used to supplement previous PSA testing or rectal examination in investigating prostate cancer. The report does not focus on prostate cancer screening or the benefits of treating prostate cancer. Likewise, we have not assessed the potential importance of the new tests in determining the seriousness of the disease, its prognosis, or the choice of treatment.

- ❑ For men with higher probability of prostate cancer, as reflected by PSA testing or rectal examination, diagnostic accuracy increases somewhat by adding the uPCA3 test. The higher the uPCA3 value, the higher the probability of cancer. A uPCA3 result above the threshold value implies a strong suspicion of prostate cancer. In some otherwise difficult-to-assess patients the test would contribute towards earlier biopsy and earlier diagnosis. The uPCA3 test cannot, however, rule out prostate cancer in men having a higher probability of the disease. Accuracy of the uPCA3 test is the same regardless of whether the individual has had a previous biopsy with negative results, or has never had a biopsy.

- ❑ The addition of the uPCA3 test to determine which patients should be biopsied involves a higher total cost than direct prostate biopsy of all men with an increased probability of prostate cancer as identified by PSA testing or rectal examination.
- ❑ The importance of the uPCA3 test in further investigation and its effects on disease course and mortality should be assessed in clinical studies. To appraise the patient benefits of routine clinical use of uPCA3, better evidence is needed regarding the value of the extra information obtained from the test results in relation to other risk factors, e.g. PSA concentration, age, rectal examination, and the results of previous biopsies.
- ❑ The scientific evidence is insufficient to appraise the diagnostic accuracy of TMPRSS2:ERG and me-GSTP1 urine tests. Further studies are needed.

Technology and target group

Prostate cancer is the most common type of cancer among Swedish men, accounting for more than 10 000 new cases annually. Of those diagnosed, approximately one in four die from the disease. Early diagnosis of prostate cancer, at a stage where the disease is not symptomatic or cannot be detected by physical examination, can be beneficial. However, early diagnosis also results in a large number of surgical interventions that provide no benefit for patients and carry a risk for negative effects.

Currently many men, on their own initiative, are examined to determine their probability of prostate cancer while having no real suspicion that they have the disease. Some call this "wild screening". The individual's probability of prostate cancer is estimated, e.g. by measuring PSA concentration in the blood and/or by rectal examination. The concentration of PSA is associated with prostate size and increases in prostate cancer. However, since cancer is not the only factor affecting PSA concentration, the PSA test provides uncertain information, especially if the

level is slightly or moderately raised. For men with a PSA concentration in the so-called "grey zone", 3 to 10 nano-grams/ml, the decision for further investigation is based on additional factors such as age, life expectancy, heredity, ethnicity, possible symptoms, results of rectal examination, possible results from earlier biopsies, the ratio of free and bound PSA in blood, and the change in PSA concentration over time. Despite the addition of these factors, it is difficult to appraise the risk in many of these men. There is a need to be able to better identify those men at greatest risk for developing clinically significant cancer and who therefore need invasive investigation by prostate biopsy.

Prostate biopsy is currently the reference method for diagnosing prostate cancer. This method has high specificity¹, which means that the test seldom indicates a tumour in healthy men. Analysis of the tissue sample from a prostate tumour also provides some information about the possible severity level of the disease and guidance for treatment. However, clinicians are often uncertain whether the identified tumour requires intensive surgical treatment or radiation (accompanied by certain risks and discomfort), or if the tumour is actually harmless. The sensitivity² of prostate biopsy is limited. Hence, there is a risk of missing tumours. For many patients, prostate biopsies are uncomfortable and painful. The procedure also involves the risk for complications such as bleeding and infection.

A particularly interesting target group for improved testing methods includes men with raised PSA concentration, but where one or more previous biopsies have not identified cancer. Due to the risk that biopsies might miss tumours, these men remain in the risk group for prostate cancer. How to monitor these men through PSA testing and further biopsy is a matter of uncertainty.

Overall, the current voluntary examination of prostate health exposes many patients to both prostate biopsy and surgical removal of the prostate, which ultimately benefits only a few patients. Avoiding unnecessary prostate biopsy is desirable, and better methods are needed to identify which of the tumours detected actually require treatment.

In recent years, several molecular genetic tests for prostate cancer have been developed: urinalysis of gene expression for PCA3 and TMPRSS2:ERG and also GSTP1 methylation levels (me-GSTP1). Several studies have shown that the amounts of these genetic products in

urine are associated with the probability of prostate cancer. Testing, which is conducted on urine samples collected in conjunction with rectal examination, is noninvasive, rapid, and not difficult for the patient. The material tested must be handled according to special protocols, but central laboratories analyse the samples. To analyse gene expression for PCA3 in urine, Gen-Probe has developed a test with a recommended threshold value of 35. The probability of prostate cancer is viewed to be greater the higher the results measured in the test. Other tests are not yet commercially available.

It is hoped that these new tests can be used to determine which of the patients with slightly to moderately raised PSA concentration actually need prostate biopsy or repeat biopsy.

Primary questions

- Can the new molecular diagnostic urine tests (uPCA3, TMPRSS2:ERG, and me-GSTP1) identify those men with slightly to moderately raised PSA concentration in blood that actually need further investigation by prostate biopsy?
- Does the addition of the uPCA3 test increase diagnostic accuracy over and above the PSA blood test in men at higher probability of prostate cancer?
- What do the tests cost? Are they cost-effective?

Diagnostic accuracy

All patients participating in the studies that we reviewed had a higher probability of prostate cancer according to the PSA blood test or rectal examination. The reference test has involved at least 8 medium-gauge needle biopsies of the prostate. Most of the included studies have used a commercially available test from Gen-Probe with a threshold value of 35 for positive³ or negative⁴ responses.

- The uPCA3 test has a sensitivity of 57% (95% CI⁵, 54 to 59), compared to prostate biopsy (moderately strong scientific evidence ⊕⊕⊕○). This means that the test missed nearly half of the men in whom prostate cancer was identified by biopsy.
- The uPCA3 test has a specificity of 74% (95% CI, 72 to 75), compared to prostate biopsy (moderately strong scientific evidence ⊕⊕⊕○). This means that 74% of the men in whom biopsy did not show tumours had negative PCA3 results.

¹ Percentage of healthy individuals that the test shows to be healthy.

² Percentage of sick individuals identified by the test.

³ Positive test results indicate disease.

⁴ Negative test results indicate absence of disease.

⁵ Confidence interval (CI).

- In the studies included in this review, a positive uPCA3 result meant that the probability of disease had increased from 31% to 50% (PPV⁶). A negative uPCA3 result meant that the probability had decreased from 31% to 21% (when NPV⁷ is 79%). The change in probability of the disease between before and after the uPCA3 test is small, but could have some importance if the result is positive.
- Based on the included studies, the diagnostic accuracy of the uPCA3 test in men who are re-biopsied after a previously negative biopsy result is the same as in men biopsied for the first time, or where the group is mixed.
- In an indirect comparison between the PSA test alone and the PSA test plus the uPCA3 test, the combination showed a somewhat higher diagnostic accuracy as measured by the area below the ROC curve⁸. The results apply only to men with higher probability of prostate cancer as indicated by a PSA test or rectal examination.
- The scientific evidence is insufficient (⊕○○○) to determine the diagnostic accuracy of the TMPRSS2:ERG and the me-GSTP1 urine tests.

Economic aspects

- The scientific evidence is insufficient (⊕○○○) to draw reliable conclusions on the cost-effectiveness of the uPCA3 test.

In Sweden, the uPCA3 test costs approximately 85% of the cost for a single round of prostate biopsies. Adding the uPCA3 test to determine which patients should be biopsied generates a higher total cost than direct prostate biopsy of the entire risk group.

⁶ Positive predictive value (PPV). The percentage of those with positive test results that are sick.

⁷ Negative predictive value (NPV). The percentage of those with negative test results that are healthy.

⁸ Receiver operating characteristic (ROC), a graphic presentation showing the performance of the test method.

Four levels are used in grading the strength of the scientific evidence on which conclusions are based:

Strong scientific evidence (⊕⊕⊕⊕). Based on high or medium quality studies with no factors that weaken the overall assessment.

Moderately strong scientific evidence (⊕⊕⊕○). Based on high or medium quality studies with isolated factors that weaken the overall assessment.

Limited scientific evidence (⊕⊕○○). Based on high or medium quality studies having factors that weaken the overall assessment.

Insufficient scientific evidence (⊕○○○). Scientific evidence is deemed insufficient when scientific findings are absent, the quality of available studies is low, or studies of similar quality present conflicting findings.

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SBU evaluates healthcare technology

The Swedish Council on Health Technology Assessment (SBU) is a national governmental agency that assesses healthcare technologies. SBU analyses the benefits, risks, and costs of different methods and compares the scientific facts to prevailing practices in Sweden. SBU's goal is to provide stronger evidence for everyone engaged in shaping the delivery of health services.

The SBU Alert reports are produced in collaboration with experts from the respective subject areas, the National Board of Health and Welfare, the Medical Products Agency, the Swedish Association of Local Authorities and Regions, and a special advisory panel (the Alert Advisory Board).

This assessment was published in 2011. Findings based on strong scientific evidence usually continue to apply well into the future. However, findings based on insufficient, limited, or contradictory evidence might have already been replaced by more recent findings.

The complete report is available in Swedish.

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