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The effect of assessing genetic risk of prostate cancer on the use of PSA tests in primary care: a cluster randomised controlled trial

Full title (200 characters)
The effect of assessing genetic risk of prostate cancer on the use of PSA tests in primary care.
Using genetic lifetime risk for prostate cancer to identify those for whom Prostate specific antigen testing is likely to be most valuable.

Short title (70 characters)
Effect of assessing genetic risk of prostate cancer PSA tests in primary care

Authors: Jan Koetsenruijter, Peter Vedsted, Maria Ervandian, Pia Kirkegaard, Michael Væth, Adrian Edwards, Torben F. Ørntoft, Karina D. Sørensen, Flemming Bro

Jan Koetsenruijter*, jankoetsenruyter@hotmail.com
Peter Vedsted**, p.vedsted@ph.au.dk
Maria Ervandian*, ervandian@dadlnet.dk
Pia Kirkegaard*, Pia.Kirkegaard@rm.dk
Michael Væth*, vaeth@pa.au.dk
Adrian Edwards*, edwardsAG@cardiff.ac.uk
Torben F. Ørntoft**, orntoft@clin.au.dk
Karina D. Sørensen**, kdso@clin.au.dk
Flemming Bro**, fbro@ph.au.dk

*Research Unite for General Practice, The Research Centre for Cancer diagnosis in Primary Care (Cap)
Author’s contributions

Conceived and designed the experiment: PV, PK, MV, AE, TØ, KS, FB
Analysed the data: JK, PV, FB
Contributed reagents/materials/analysis tools: JK, ME, PV, PK, MV, AE, TØ, KS, FB
Lead drafting of the paper: JK, ME, PV, AE, KS, FB
All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work’s accuracy or integrity.

Conflict of interest statements

All authors have nothing to disclose.
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Number of figure: 1
Abstract (280 words)

Background: Assessing genetic lifetime risk for prostate cancer has been proposed as a means of risk stratification to identify those for whom Prostate Specific Antigen (PSA) testing is likely to be most valuable. However, it is unclear if introducing a genetic test influences decisions about the use of PSA tests. The Procaris project aimed to test the effect on future PSA testing of introducing a genetic test for life-time risk of prostate cancer in general practice.

Methods: We performed a cluster randomised controlled trial, with randomisation at the level of general practices. In intervention practices, men were offered an additional genetic test (based on genotyping risk single nucleotide polymorphisms) to the standard PSA test, informing them about their lifetime genetic risk of prostate cancer, distinguishing between ‘average’ risk and high risk. The primary outcome was the proportion of men having a repeated PSA test within two years. A multilevel logistic regression model was used to test the association.

Findings: In total, 146 practices participated, 73 in each study arm. In intervention practices 3558 men were recruited and in control practices 4242. Of the eligible men, 1235 (34.7%) received the genetic test. We found no significant difference (p=0.53) in the proportion of PSA tests between control and intervention practices. Men who had a high genetic risk had a higher propensity for repeated PSA test within two years than men with an average genetic risk (OR = 8.94, p<0.01).

Interpretation: Providing GPs with access to a genetic test to assess life-time risk of prostate cancer did not reduce the overall number of future PSA tests. Among men who had a test, knowledge of the genetic risk significantly influenced future PSA testing.
Introduction

Prostate cancer is the most common cancer among men in Europe, affecting about 190,000 men for the first time every year and causing about 80,000 deaths. A commonly used method for early detection of prostate cancer is the Prostate Specific Antigen (PSA) test, although this method has limited accuracy. This results in both failure to detect genuinely aggressive cancers and over-detection and over-treatment of indolent prostate cancers. Currently, although still debated, population-based screening using the PSA test is not advised. Opportunistic screening and testing is increasingly common however, but with the same uncertain benefits and some risks, including risk of over-diagnosis. Therefore, there is interest in whether PSA testing can be targeted to those for whom it may be more valuable.

Risk stratification is proposed as a strategy to reduce the overall number of men having the PSA test and to improve the benefit-to-harm ratio by targeting those most likely to benefit. This is already advocated in guidelines assessing risk by family history. Now, genetic markers offer potential to improve risk assessment for developing prostate cancer. So far, scientific advances in genome-wide association studies have identified more than 100 genetic variants for higher prostate cancer risk, the so-called single nucleotide polymorphisms (SNPs). It has been estimated that the currently known risk-SNPs together explain approximately 33% of the familial risk of prostate cancer in populations of European ancestry, and that the top 10% of men in the risk distribution have a 2.9-fold increased relative risk of prostate cancer, compared with the general population. Retrospective studies comparing non-genetic risk prediction models for the detection of prostate cancer with models containing SNP information showed that genetic models had higher specificity than the non-genetic models based on PSA level, age and family history. Despite the potential benefits, few studies have used genetic prostate cancer risk assessment in the clinical setting as a tool for improving use of PSA and diagnosing prostate cancer, particularly in general practice where most symptoms are presented and testing takes place. It can be hypothesised that the number of
PSA tests would increase in the small group of men with increased risk and could be reduced in the large group of men with 'average' risk.\textsuperscript{13}

We aimed to test the effect on future PSA testing of introducing a genetic test for life-time risk of prostate cancer among men with a normal PSA test in general practice.

\textbf{Methods}

\textit{Study design}

We performed a cluster randomised controlled trial with randomisation at the level of general practices. Block randomisation was applied to balance groups with respect to number of doctors in a practice. The study follows the CONSORT statement for reporting randomised trials and has been described in detail previously.\textsuperscript{13} This study is registered with ClinicalTrials.gov, number NCT01739062.

\textit{Setting and participants}

The study took place from February 2013 to November 2014 in Central Region Denmark. This is one of five regions in Denmark and has 1.3 million inhabitants and about 850 general practitioners (GPs) in 400 practices. All Danish residents have free access to GPs who serve as gatekeepers to the rest of the health care system. Over 98\% of all citizens are registered with a specific practice. It is mandatory for GPs to use electronic patient records, and test requisitions and test results are transferred electronically.\textsuperscript{14} All Danish citizens have a unique personal identifier number which is registered for all contacts and investigations and which makes it possible to link all data on individual basis.\textsuperscript{15}

Men were eligible for participation if they were aged 18-80 years, registered with one of the randomised practices and had a normal PSA test at inclusion. A normal PSA test was defined as a value below 3.0 ng/ml
for men below age 60, below 4.0 ng/ml for men aged 60-70, and below 5.0 ng/ml for men aged 70 or above. Men were excluded if they had an elevated PSA level at inclusion or within the previous two years, known prostate or bladder disease, or a current or previous prostate cancer diagnosis.

In this trial, men of non-European ancestry were included but not offered the genetic test, as genetic risk estimates were based on data from European-descent population studies only (Supplementary file 1). For safety reasons, men in the intervention group who had more than one close relative with a prostate cancer diagnosis were advised to undergo systematic screening with PSA tests according to current clinical guidelines in Denmark. Both groups however were still included in the intention-to-treat analysis. The GP determined eligibility for the genetic test in the clinical setting based on criteria incorporated into the web-based test-ordering system.

**Intervention**

In addition to a PSA test, men in intervention practices were offered an additional genetic risk assessment. Based on genotyping of 31 risk loci/SNPs (Supplementary file 1), individual lifetime prostate cancer risk was calculated for each man after adjusting for prostate cancer family history. Lifetime risk scores were dichotomised into an ‘average’ risk (<30%) and ‘high’ risk (≥30%) categories, thus conservatively adhering to the Danish recommendations to screen individuals who (based on family history) have an estimated 33% lifetime risk of being diagnosed with prostate cancer.

The procedure was as follows: when a man was to have a PSA test, and met the inclusion criteria, the GP informed him about the study and provided written information. If he consented to participate, the GP drew an additional 4 ml EDTA-stabilized blood sample, which was sent to the laboratory together with an online request for a genetic risk assessment, including information about the man’s age and family history.
of prostate cancer. Within 2-6 weeks, the laboratory analysed the genetic test and sent the result electronically to the intervention practice GP, with one of the following recommendations:

High lifetime risk:

“The patient belongs to a group with increased risk of developing prostate cancer in the future. If the patient develops prostate cancer in the future, in most cases, the cancer will be slow growing. For early detection, the patient is encouraged to have a yearly PSA test”.

Average lifetime risk:

“The patient belongs to a group of patients at average lifetime risk of getting a prostate cancer diagnosis. It is not considered necessary or beneficial for the patient to have more PSA tests in the future, unless the patient develops urinary tract symptoms or one or more of his relatives develops prostate cancer”.

If the risk assessments could not be performed because family history was unclear or unknown, a risk estimate was provided, doubling the risk of someone with “no relatives with prostate cancer”. If this estimate was >30%, the patient was advised to enter a screening program and received the following advice: “The risk for developing prostate cancer in the future cannot be estimated due to missing information for family history. However, the patient may benefit from a screening program with PSA tests, with a view to early diagnosis”.

Once the practice received the genetic risk assessment results, the GP or other practice personnel informed the patient about the result. In case of questions, both intervention practice personnel and men could contact a project telephone hotline to the researchers. Each intervention practice also received written information with recommendations about follow-up PSA testing according to current guidelines and information about the benefits and shortcomings of genetic risk assessment as a tool to support decision-making about PSA-testing for prostate cancer.
The GPs were remunerated with an additional 142 Danish krone (≈ €9) per consultation, which covered the additional work in relation to information and blood sampling. Control practices performed care as usual and received no further information or compensation. The initial intervention period ran from February 2013 until December 2013. However, because the GPs appreciated the opportunity to offer the genetic test, it was made available for them to include men for another year until November 2014. We used the full period (February 2013 - November 2014) for our analyses.

**Outcomes**

The primary outcome was the proportion of men who had a PSA test within two years after a normal PSA test result at inclusion. Two years of follow-up was chosen as this was considered a reasonable screening interval for healthy adults. Although men were included only through GP practices, tests requested by hospitals and private specialist clinics were also taken into account as a PSA test in the follow-up period.

Secondary outcomes were the proportion of men with an elevated PSA test and the proportion of men referred for prostate biopsies. Data about the date and level of the PSA test were collected from the regional clinical laboratory information system (LABKA), which keeps results for all PSA tests in the region. Prostate biopsies were identified in the Danish National Patient Register.

**Participant characteristics**

Information on age, marital status (married, widower, divorced, and never married), highest achieved education (<10 years (primary and lower secondary school), 10–12 years (upper secondary school or vocational training), >12 years (higher education)), household income adjusted for number of persons in the household (in tertiles), and working status (employed, unemployed, pensioner, or other) was collected from registries at Statistics Denmark.
Practice characteristics

To account for possible differences between practices at baseline, we calculated per practice the number of PSA tests per 1000 men aged >40 years in the year before the intervention started (2012).

Sample size

We expected that 75% of the men in the intervention group would receive the genetic prostate cancer risk assessment, and we estimated that 88% of the men would have an average genetic risk. The sample size was based on an expected reduction of PSA test by 50% in the group with an average genetic risk. This would result in a reduction from 23% to 15% in the overall proportion of men with a PSA test in the follow-up period. This required the inclusion of 1244 men in the intervention arm and, allowing for a design effect (intra class correlation) of 1.2, provided study power of 90% with alpha of 5%.

Statistical analysis

Data were analysed using Stata (release 14). For all statistical tests, two-sided hypothesis testing with an alpha of 0.05 was applied. Primary analyses were based on an ‘intention-to-treat’ principle for both primary and secondary outcomes.

A logistic multilevel model with men nested within practices was used to estimate odds ratio (OR) as the association between exposure (being in an intervention practice) and outcome. In addition, we performed a time-to-event analysis using a Cox proportional hazards regression model to include the differences in time to the PSA test.

Analyses were adjusted for participant characteristics (age, education and household income) and for the number of PSA tests per 1000 men aged >40 years per practice at baseline. Missing values on background
characteristics (500 cases, 6.4%) were imputed using a multiple imputation procedure based on the ‘MICE’ approach.\textsuperscript{21}

Sub-group analyses were performed on men in intervention practices, comparing men with and without a genetic test and on men with a genetic test comparing men with a high-risk genetic profile to men with a normal lifetime risk in relation to outcomes.

To study the difference in uptake of the intervention, we calculated the actual intra class correlation (ICC) for the chance of receiving a genetic test.

Men who died of non-prostate cancer related causes or moved within the follow-up period of two years were excluded from the analysis.

\textit{Ethical approval and considerations}

The study was conducted according to the Helsinki Declaration principles. It has been notified to the Danish Data Protection Agency (Journal no. 2011–41–6904) and collection of data was handled according to their guidelines. The study has obtained permission from the Danish Scientific-Ethical Committee (Journal no. 1-10-72-43-12).

All participants provided informed consent. Men in the intervention group received printed information from the GP and could withdraw from the study at any time and have their blood sample destroyed and project data deleted.

\textbf{Results}
Study population

After excluding practices (n=9) that were used for an initial pilot to set-up to test the project infrastructure, 146 (36.5% of total) practices in the region accepted the invitation to participate and were randomised (Figure 1).

In the intervention period, 5836 men in the intervention practices and 6750 men in the control practices received at least one PSA test (Figure 1). After applying the exclusion criteria, 7800 eligible men were included in the analyses (intervention, n=3558; control, n=4242).

Figure 1. Flowchart

Men who received a PSA test were similar between intervention and control practices on education, income, marital status, and working status (Table 1). In intervention practices, fewer men aged <55 (22.9% versus 27.1%) and more men aged >69 years (25.6% versus 21.6%) were eligible for inclusion. Intervention practices had on average slightly more men aged >40 years in their practices than control practices (means 714.4 and 676.0, respectively) and performed fewer PSA tests per 1000 men per year at baseline (86.5 versus 104.7).
Table 1. Description of practice and participant sample at baseline

<table>
<thead>
<tr>
<th></th>
<th>Control (n=4242)</th>
<th>Intervention (n=7800)</th>
<th>Total (n=7800)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Full sample</td>
<td>Received genetic test</td>
<td>Did not receive genetic test</td>
</tr>
<tr>
<td>Cluster level (GP practices)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average number of men age &gt;40 per practice (SD)</td>
<td>676.0 (412.5)</td>
<td>714.4 (387.1)</td>
<td>695.3 (398.9)</td>
</tr>
<tr>
<td>Number of PSA tests per 1000 men age &gt;40 at baseline (SD)</td>
<td>104.7 (95.8)</td>
<td>86.5 (67.5)</td>
<td>95.5 (82.9)</td>
</tr>
<tr>
<td>Number of practices</td>
<td>73</td>
<td>73</td>
<td>146</td>
</tr>
</tbody>
</table>

Individual level (men)

<table>
<thead>
<tr>
<th>Age (%)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>≤54</td>
<td>27.1</td>
<td>22.9</td>
<td>25.4</td>
<td>21.5</td>
</tr>
<tr>
<td>55-59</td>
<td>13.9</td>
<td>13.3</td>
<td>15.0</td>
<td>12.4</td>
</tr>
<tr>
<td>60-64</td>
<td>17.5</td>
<td>17.1</td>
<td>19.0</td>
<td>16.1</td>
</tr>
<tr>
<td>65-69</td>
<td>19.9</td>
<td>21.1</td>
<td>19.1</td>
<td>22.1</td>
</tr>
<tr>
<td>70+</td>
<td>21.6</td>
<td>25.6</td>
<td>21.4</td>
<td>27.9</td>
</tr>
</tbody>
</table>

Highest educational level (%)

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 yrs (primary and lower secondary school)</td>
<td>28.2</td>
<td>28.1</td>
<td>23.1</td>
<td>30.9</td>
</tr>
<tr>
<td>Education Level</td>
<td>10–12 yrs (upper secondary school or vocational training)</td>
<td>&gt;12 yrs (higher education)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>---------------------------------------------------------</td>
<td>-----------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>51.8 51.2 53.0 50.2</td>
<td>20.0 20.7 23.9 18.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>20.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Household income (tertiles, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>33.8 32.8 24.8 37.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>33.2 33.5 35.5 32.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>33.0 33.7 39.7 30.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital status (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>72.1 74.4 78.9 72.0</td>
<td>73.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Widower</td>
<td>3.6 3.3 2.5 3.8</td>
<td>3.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divorced</td>
<td>10.7 10.5 8.7 11.5</td>
<td>10.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never married</td>
<td>13.6 11.8 9.9 12.7</td>
<td>12.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working status (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>51.5 51.4 58.5 47.6</td>
<td>51.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>2.2 1.7 1.3 1.8</td>
<td>2.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pensioner</td>
<td>42.8 44.0 37.6 47.5</td>
<td>43.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3.5 2.9 2.6 3.1</td>
<td>3.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Intervention group only: received genetic test versus did not receive test (chi-square test)

* p<0.01
Out of the 3558 eligible men in intervention practices, 1235 (34.7%) received a genetic test (Figure 1). This percentage ranged from 0% to 82% between practices (intra-class correlation coefficient (ICC) = 0.37). Men who received the genetic test were younger (\(p<0.01\)), more highly educated (\(p<0.01\)), more often married (\(p<0.01\)) and employed (\(p<0.01\)) and had higher incomes (\(p<0.01\)) than men who did not receive the genetic test (Table 1).

Of the men who received a genetic test, 1047 (84.8%) had an average genetic risk for prostate cancer and 136 (11.0%) had a high risk (Table 2). For 52 men (4.2%) the genetic risk could not be calculated or was not traceable in the registries. In further analyses they are included as a separate category ‘Unknown risk’.

Effect of genetic test on future PSA tests

Two years after inclusion, a total of 1218 men (34.2%) in the intervention practices and 1628 (38.4%) men in the control practices had a PSA test (OR = 0.95, 95% CI=0.78-1.14, \(p=0.56\)) (Table 2). In the intervention group, men with an average genetic risk (24.9%) had fewer PSA tests than men without a genetic test (37.5%; OR = 0.65, 95% CI=0.54-0.78, \(p<0.01\)) while men with a high genetic risk had more (75.0%; OR = 5.96, 95% CI=3.96-8.97, \(p<0.01\)).

The proportion of PSA tests that resulted in an elevated value was similar between the control and intervention group (2.3% vs 2.2%) (OR = 1.01, 95% CI=0.71-1.43, \(p=0.96\)). Higher percentages were found in the group with a high genetic risk (6.6%) than in men without a genetic test (2.2%) (OR = 3.31, 95% CI=1.57-6.97, \(p<0.01\)).

In the subgroup of men that had a PSA test in the follow-up period, 6.2% of those tests were elevated (not shown). This was similar between intervention (6.4%, 78/1218) and control (6.0%, 97/1628) practices (OR =
1.08, p=0.62). No significant difference was found between men with a high genetic risk (8.8%, 9/102) and men with an average genetic risk (6.1%; 16/261, OR = 1.49, p=0.36).

No difference between control and intervention was found on the numbers of biopsies (both 0.2%).
Table 2. Unadjusted primary and secondary outcomes after two years follow-up

<table>
<thead>
<tr>
<th></th>
<th>Control (n=4242)</th>
<th>Intervention (n=3558)</th>
<th>OR (^a) (95% CI, sign.)</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men with a PSA test, N (%)</td>
<td>1628 (38.4%)</td>
<td>1218 (34.2%)</td>
<td>0.95 (95% CI = 0.78-1.14)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men with an Elevated PSA test, N (%)</td>
<td>97 (2.3%)</td>
<td>78 (2.2%)</td>
<td>1.01 (95% CI = 0.71-1.43)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Control vs. intervention, \(^b\) Average risk vs. no genetic test, \(^c\) High risk vs. no genetic test

Adjusted analysis

After adjusting for confounders, no significant effect was found of the intervention on the number men with a PSA test at two years follow-up (OR = 0.95, p=0.53) (Table 3). The number of PSA tests per 1000 men aged >40 per practice at baseline (OR = 1.02, p<0.01 per 10 extra tests), older age (increasing OR per age group), and a high income (OR = 1.28, p<0.01 compared to the low-income group) were associated with a higher chance of a future PSA test (Table 3).

The time-to-event (i.e. time to repeated PSA test) analysis showed no significant difference between control and intervention practices (p=0.36). However, for those men who had a PSA test, this was done on average 21 days later in intervention practices than in control practices (483 days, (SD=188) versus 462 (SD=178)) (p=0.01) (not in table).
Within intervention practices, men with an average genetic risk had a significantly lower chance of having a future PSA test than men who did not receive the genetic test (OR = 0.62, p<0.01), while men with a high genetic risk had a significantly higher chance (OR = 8.94, p<0.01) (Table 3) and the difference between men with an average and high genetic risk was also statistically significant (OR = 14.51, p<0.01) (not in table).

The number of PSA tests with an elevated value followed the same pattern; no significant difference was found between intervention and control practices (OR = 1.08, p=0.65).
Table 3. Primary and secondary outcomes after 2 years follow-up; adjusted multilevel logistic regression model (OR)

<table>
<thead>
<tr>
<th></th>
<th>Men with a PSA tests</th>
<th>Men with an elevated PSA tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total population</td>
<td>Intervention group only</td>
</tr>
<tr>
<td></td>
<td>(n=7800)</td>
<td>(n=3558)</td>
</tr>
<tr>
<td><strong>Cluster level (practices)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention (ref = control)</td>
<td>0.95</td>
<td>1.08</td>
</tr>
<tr>
<td>Number of PSA tests per 1000 men age &gt;40 at baseline (x10)</td>
<td>1.02**</td>
<td>1.02**</td>
</tr>
<tr>
<td><strong>Individual level (men)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic test result (ref = No genetic test)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average risk</td>
<td>0.62**</td>
<td>0.64</td>
</tr>
<tr>
<td>High risk</td>
<td>8.94**</td>
<td>4.06**</td>
</tr>
<tr>
<td>Unknown risk</td>
<td>2.46*</td>
<td>3.41</td>
</tr>
<tr>
<td><strong>Age (ref ≤54)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55-59</td>
<td>1.98**</td>
<td>2.11**</td>
</tr>
<tr>
<td>60-64</td>
<td>2.59**</td>
<td>2.56**</td>
</tr>
<tr>
<td>65-69</td>
<td>3.41**</td>
<td>3.31**</td>
</tr>
<tr>
<td>70+</td>
<td>4.01**</td>
<td>4.17**</td>
</tr>
<tr>
<td>Highest educational level (ref &lt;10 yrs)</td>
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<tr>
<td>Education Level</td>
<td>10–12 yrs (upper secondary school or vocational training)</td>
<td>&gt;12 yrs (higher education)</td>
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<tr>
<td></td>
<td>1.12 1.07 1.19 1.23</td>
<td>1.10 1.09 1.25 1.63</td>
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* p<0.05  ** p<0.01
Discussion

Main findings

The introduction of the genetic risk assessment in general practice did not affect the overall number of men with a normal PSA test receiving a future PSA test within two years. Uptake of the genetic test was about one third and within this group, more men with a high lifetime prostate cancer risk had a further PSA test compared with men at an average lifetime risk. Men with an average lifetime risk also had fewer PSA tests compared to men who did not receive the genetic test.

Strengths and weaknesses

Using routinely collected data from registries linked with the personal identifier number ensured complete follow-up and allowed us to use all initially included men in the analyses. The follow-up period of two years was not long enough to draw final conclusions about the effect of this intervention on the diagnosis or mortality rate of prostate cancer.

The study was conducted in routine practice and with limited support to the GPs. Selection bias was evident for the limited proportion of eligible men who received the genetic test, whether by GPs and/or the men consulting, resulting in a relatively young and high income sub-sample offered and accepting the test. This may, for example, have comprised men who were more responsive to the information about lifetime risk. Our study does not provide information about the selection mechanism behind the low uptake. It may be more due to low uptake among some GPs (ICC between practices of 0.37, range of uptake from 0-82%) rather than participant influences. However, the intention-to-treat analysis minimised this selection bias concerning the primary outcome analysis.

Comparison with other studies
Until now, a genetic test to assess the risk for prostate cancer has not been tested in a GP setting and thus no direct comparisons can be made. The Stockholm-1 cohort study tested whether a genetic model based on 36 SNPs could reduce the number of biopsies compared to a non-genetic model based on age, PSA, free-to-total PSA, and family history. Their genetic model reduced the number of biopsies more than the non-genetic model. The proportion of men with an elevated follow-up PSA level in our study population is consistent with downstream effects in previous studies. The association that we found between the genetic test result and the number of elevated follow-up PSA tests for those at high risk, and reduced tests for those at average risk, illustrates the potential for downstream effect of the intervention. Given the relatively low levels of implementation, however, overall downstream effects were not shown in this study in terms of referrals for prostate biopsy.

It is a complex decision whether to have a PSA test, but studies on decision aids have shown that better informed decisions can result in fewer men receiving PSA tests. We do not know how the GPs used the test results and how they conveyed the result to the men, but other studies suggest that genetic risk assessment increases clinicians’ confidence in managing familial cancer. Recent studies show that both men and GPs still struggle with PSA screening. In a study among men who had had direct-to-consumer genome-wide profiling to assess prostate cancer risk, Bloss et al. found that men had a 20% higher intention to take PSA tests with a high lifetime risk. We found that 75% of the men with a high risk actually had a test performed within two years, suggesting that men have acted on such knowledge (although the GP may also have influenced such decisions quite significantly) and there is potential for risk stratification to assist routine practice.

**Implications for practice**

Implementing the test in routine practice, we did not find an effect on future PSA testing for all men in the intervention practices as a whole. It is important to gain insight into the process of implementation. If
uptake continues to be low for either GP or participant reasons, there will be no impact of such risk stratification at population level, even if there are significant effects in sub-groups. However, if barriers to implementation can be removed, further evaluations may show a similar more appropriate targeting of PSA testing to those at high risk, and perhaps an overall reduction of testing. It is important to identify the barriers, address them, and to reach a firm conclusion whether or not to make a genetic test for lifetime risk of prostate cancer available in general practice.

Further research

This study showed that it is feasible to integrate a genetic prostate cancer risk assessment in a general practice setting. So far, this has not resulted in an overall reduction in the number of future PSA tests. However, the differences in numbers of future PSA tests between normal and high lifetime risk groups in those taking up the test suggests that further study is indicated as to whether these effects are replicated, sustained, and large enough to affect an important range of health services research outcomes such as quality-of-life, referrals, biopsies, diagnoses of prostate cancer, mortality, impact on over-diagnosis (of indolent pathologies) and resource use effects. Further research is also necessary to explore factors that facilitate or hinder implementation of providing this genetic test to men, and how it is used by men (and family members) in deciding on future screening or testing intentions. Based on this, future interventions could be developed that support GPs with the integration of genetic tests in routine practice and men with making informed decisions.

Conclusion

Offering a genetic test to assess men’s life-time risk of prostate cancer did not reduce the overall propensity of repeated PSA tests within a two year period among men with a normal PSA. However, knowledge of genetic risk reduced the number of PSA tests among those at average risk and increased the number of PSA tests among those at high risk. Further research is needed to examine how uptake of the
test can be supported and whether such an increase can effectively reduce the number of overall future PSA tests and the consequent downstream effects.

Acknowledgments

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