Reducing overdiagnosis by polygenic risk-stratified screening: findings from the Finnish section of the ERSPC

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Background: We derived estimates of overdiagnosis by polygenic risk groups and examined whether polygenic risk-stratified screening for prostate cancer reduces overdiagnosis.

Methods: We calculated the polygenic risk score based on genotypes of 66 known prostate cancer loci for 4967 men from the Finnish section of the European Randomised Study of Screening for Prostate Cancer. We stratified the 72,072 men in the trial into those with polygenic risk below and above the median. Using a maximum likelihood method based on interval cancers, we estimated the mean sojourn time (MST) and episode sensitivity. For each polygenic risk group, we estimated the proportion of screen-detected cancers that are likely to be overdiagnosed from the difference between the observed and expected number of screen-detected cancers.

Results: Of the prostate cancers, 74% occurred among men with polygenic risk above population median. The sensitivity was 0.55 (95% confidence interval (CI) 0.45–0.65) and MST 6.3 (95% CI 4.2–8.3) years. The overall overdiagnosis was 42% (95% CI 37–52) of the screen-detected cancers, with 58% (95% CI 54–65) in men with the lower and 37% (95% CI 31–47) in those with higher polygenic risk.

Conclusion: Targeting screening to men at higher polygenic risk could reduce the proportion of cancers overdiagnosed.

At 13 years of follow-up, the European Randomised Study of Screening for Prostate Cancer (ERSPC) showed a 21% relative reduction in prostate cancer mortality in favour of screening, with one prostate cancer death prevented and 27 additional cases detected per 781 men invited to screening (Schroder et al, 2014). The number needed to detect and the number needed to invite to prevent one prostate cancer death were less at 13 years than at 9 and 11 years of follow-up. Despite the improvement in the absolute benefit of screening, concerns about the negative consequences of screening, mainly overdiagnosis and treatment of overdiagnosed cancers, remain obstacles for large-scale screening. An overdiagnosed cancer is defined as one that would not have presented
clinically in a person’s lifetime in the absence of screening. Developing methods to reduce overdiagnosis remains crucial for diminishing the adverse effects of screening.

To date, genome-wide association studies have identified 100 prostate cancer susceptibility loci, which explain ~33% of the familial risk of prostate cancer in population of European ancestry (Al Olama et al, 2014). Assuming a log-additive model of interaction between loci, the currently known loci define a polygenic risk profile that could be used for risk stratification (Pharoah et al, 2008; Pashayan et al, 2011). Men at 90th and 99th percentile of the risk distribution are at 2.9- and 5.7-fold increased risk for prostate cancer compared with the average population (Al Olama et al, 2014).

A personalised screening strategy based on age and genetic risk has the potential to improve the efficiency of the screening programme (Pashayan et al, 2011) and reduce its adverse consequences (Pashayan et al, 2015). A mathematical modelling study using UK-based prevalent screen and incident cancer data has shown that the proportion of screen-detected cancers likely to be overdiagnosed varies inversely by polygenic risk (Pashayan et al, 2015). However, the estimates of overdiagnosis were based on mean sojourn time (MST) and test sensitivity derived from the published literature. Using screening trial data from the Finnish section of ERSPC, this study aims to estimate MST and sensitivity and then use these estimates to derive the probability of overdiagnosis by polygenic risk. This is to examine whether a risk-stratified screening strategy reduces the proportion of cancers overdiagnosed.

### MATERIALS AND METHODS

**Study participants.** The Finnish Prostate Cancer Screening Trial is the largest component of the ERSPC. The trial population and the protocol have been described in detail elsewhere (Finne et al, 2003). Briefly, during 1996 and 1999, a total of 80 458 men aged 55, 59, 63, and 67 years were identified from the Finnish Population Registry and of whom 80 176 were randomised to either the screening arm (N = 31 875) or the control arm (N = 48 301). Men in the screening arm were invited for serum prostate specific antigen (PSA) testing every 4 years up to three times until age 71 years. The study protocol was approved by the ethical committees of Helsinki University Hospital and Tampere University Hospital. Figure 1 presents the number of men in the trial and cancers detected.

Men were referred for transrectal ultrasound-guided biopsy if the PSA value was $\geq 4.0$ ng ml$^{-1}$ or the PSA was 3.0–3.99 ng ml$^{-1}$ with suspicious findings on digital rectal examination (in 1999–1998) or with free/total PSA ratio $<0.16$ (since 1999). Initially, sextant biopsies were used, and from 2002, 10 to 12 biopsy cores were taken.

Incident cancers diagnosed among the controls and the non-participants, and interval cancers were identified through record linkage to the nationwide population-based Finnish Cancer Registry, which has almost complete coverage of all solid cancers diagnosed in Finland (Teppo et al, 1994). An interval cancer was defined as cancer diagnosed in the interval 1–4 years after screening attendance. Cancers in non-participants and in those diagnosed more than 4 years after the previous screen were not regarded as interval cancers. Cancers that were not diagnosed through organised screening were referred to as clinically diagnosed.

Prostate cancer was classified as localised disease with tumour-node-metastasis (TNM) stage T1-2 N0 M0; and advanced disease (regional-distant) with stage T3 and above or any T N1 M1; as non-aggressive tumour, Gleason score $<7$, and aggressive tumour, Gleason score $\geq 7$.

The follow-up for this analysis was until 31 December 2011 and the median duration of follow-up was 13 years.

**Genotyping and quality control.** At the time of genotyping, there were 70 prostate cancer susceptibility variants identified through genome-wide association studies. The analysis was based on 66 of these variants (Supplementary Table 1S) for a sample of the trial participants, 1089 men with prostate cancer and 3878 men without prostate cancer. Genotyping platform (Wang et al, 2009; Eeles et al, 2013) and quality control are described in the Supplementary File.

### Polygenic risk score and absolute risk calculations.

A polygenic risk score (PRS) for each individual was calculated as:

$$
PRS_i = \sum_{j=1}^{n} \beta_j x_{ij}
$$

where $\beta_j$ is the per-allele log-odds ratio for locus $i$, $x_{ij}$ represents the number of risk alleles (i.e., 0, 1 or 2) carried by each individual j at locus $i$, and $n$ is the number of loci.

The risk conferred by each of the variants is assumed to be allele dose-dependent with a multiplicative (log-additive) effect on a relative-risk scale (Pharoah et al, 2002). Under the multiplicative model the distribution of polygenic risk in the population at birth follows the normal distribution when relative risk is plotted on a logarithmic scale, with mean, $\mu$, and variance $\sigma^2$. We set the mean, $\mu = -\sigma^2/2$, so that the mean relative risk in the population at birth is equal to unity. The distribution of relative risk among cases at young ages is also log-normal with the same variance, but with larger mean, $\mu + \sigma^2$ (Pharoah et al, 2002).

### Estimating overdiagnosis

**Mean sojourn time and sensitivity of PSA.** Assuming exponential distribution of sojourn time, we estimated the sensitivity and the MST by the maximum likelihood method of Walter and Day (Walter and Day, 1983). The likelihood was evaluated over a two-dimensional grid of values of sensitivity, $S$, and of inverse of MST, $\lambda$. The observed incidence of interval cancers was assumed to follow a Poisson process with an expected incidence of interval cancer that depends on $S$ and $\lambda$, as such:

$$
I_{\text{int}}(t) = I'(1-S) + I' S \left\{ e^{-\lambda t} - \frac{1}{\lambda} \right\}
$$

where $I_{\text{int}}(t)$ is the expected incidence rate of interval cancers at time $t$, and $I'$ is the underlying incidence rate of prostate cancer in the absence of screening, derived from the observed incidence rate in the control arm. Here, person-years at risk were calculated from time of randomisation to time of prostate cancer diagnosis, death or censoring date (31 December 2011), whichever occurred first.

To calculate the 95% confidence level (CI), we identified the combinations of values of $S$ and $\lambda$ for which the log likelihood was 1.92 less than the maximum value (Day and Walter, 1984).

As the maximum likelihood approach is based on interval cancers, the derived estimates of $S$ and $\lambda$ refer to non-overdiagnosed cancers. Also, given how interval cancers were defined in this study, the sensitivity refers to episode sensitivity, that is, performance of the test and the diagnostic work up (Hakama et al, 2007).

**Expected number of non-overdiagnosed screen-detected cancers.** Given $S$ and $\lambda$, we estimated the expected prevalence and incidence of non-overdiagnosed cancers at first and subsequent screens, as such:

Expected prevalence:

$$
P = \frac{I' S}{\lambda}
$$

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Expected incidence at second screen:

\[ I' = IS \left( \frac{(1-S)e^{-\lambda t}}{\lambda} + \frac{(1-e^{-\lambda t})}{\lambda} \right) \] (4)

Expected incidence at third screen:

\[ I'' = S \left( \frac{I' (1-S)}{S} + I' \frac{(1-e^{-\lambda t})}{\lambda} \right) \] (5)

We applied the expected prevalence and incidence rate to the number of men screened at each round, and estimated the expected number of non-overdiagnosed cancers. If \( O \) is the observed number of screen-detected cancers, and \( E \) is the expected number of non-overdiagnosed cancers, then the proportion of screen-detected cancers likely to be overdiagnosed would be \( \frac{O - E}{O} \).

**Estimation of overdiagnosis by PRS.** The PRS was available on subsample of men with screen-detected cancers, interval cancers, and incident cancers, and on subsample of men without cancer. We stratified men with and without prostate cancer into two risk groups: below and above 50th percentile of polygenic risk distribution among the population, hereafter referred to as lower and higher risk groups, respectively. In the subsamples, the proportions in the higher risk groups are shown in Table 1. We used these proportions as sampling fractions to derive the likely proportion of the study population with and without prostate cancer in the lower and higher risk groups. To estimate the baseline incidence rate of prostate cancer by polygenic risk groups, we derived the relative rate of clinical cancers in the two risk groups using information on interval cancer as such:

\[ \frac{R_h}{R_l} = \frac{n_h/N_h}{n_l/N_l} \] (6)

where \( n_h \) and \( n_l \) are the number of interval cancers in the higher and lower risk groups, respectively; and \( N_h \) and \( N_l \) are the number of men screened in the higher and lower risk groups, respectively. Then the overall rate would be:

\[ I' = \alpha_p R_h + (1-\alpha_p) R_l \] (7)

where \( \alpha_p \) is the sampling fraction for men free of cancer in the screening arm and in the higher risk group.
We derived separate estimates of overdiagnosis for those in the lower and higher risk groups by repeating the steps used to estimate the overall overdiagnosis.

**Sensitivity analysis.** In the Finnish Prostate Cancer Screening Trial, 19% of men in the control group had PSA test in the first 4 years. In a sensitivity analysis, we estimated the baseline incidence rate after excluding men with cancer detected following PSA testing, and re-estimated overdiagnosis by polygenic risk groups.

### RESULTS

The distribution of PRS based on 66 prostate cancer susceptibility loci had mean (scaled mean) of −0.16 (−0.198) and variance of 0.40 among men with no prostate cancer and mean of 0.30 (0.20) and variance of 0.40 among men with the cancer. There was no statistically significant difference in the mean PRS of men with screen-detected vs clinically diagnosed cancer (t-test \( P = 0.137 \)) (Table 2). The polygenic risk scores at the 25th, 50th, and 75th percentiles of the risk distribution among men with no prostate cancer accounted for 17%, 26%, and 48% of the cases, respectively. Thus, men in the high-risk group (above the 50th centile) accounted for 74% of the cases.

The PRS was available on 35% of men with screen-detected cancer and 9% of men with cancer in the control arm. The proportions of men with screen-detected cancer with advanced stage, Gleason score \( \geq 7 \), or PSA \( \geq 4 \) were comparable between the trial participants overall and the subsample of men with PRS. However, out of clinically diagnosed cancers, the subsample with PRS had lower proportion of cancers with advanced stage or Gleason score \( \geq 7 \) compared with all clinically diagnosed cancers (Table 3).

**Table 1. Proportion of the study population with PRS and of those in the higher risk group**

<table>
<thead>
<tr>
<th>Screening arm</th>
<th>No. (%) with PRS</th>
<th>No. (%) with PRS in the higher risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men with no prostate cancer ( N = 21,030 )</td>
<td>3877 (18.4)</td>
<td>1930 (49.8)</td>
</tr>
<tr>
<td>Screen-detected cancer at first round of screening ( N = 686 )</td>
<td>173 (25.2)</td>
<td>131 (75.7)</td>
</tr>
<tr>
<td>Screen-detected cancer at subsequent rounds of screening ( N = 960 )</td>
<td>406 (42.3)</td>
<td>285 (70.2)</td>
</tr>
<tr>
<td>Interval cancer ( N = 525 )</td>
<td>115 (21.9)</td>
<td>92 (80.0)</td>
</tr>
<tr>
<td>Clinically diagnosed cancer ( &gt; 4 ) years after last screen ( N = 565 )</td>
<td>34 (6.0)</td>
<td>25 (73.5)</td>
</tr>
<tr>
<td>Non-participants with clinically diagnosed cancer ( N = 562 )</td>
<td>22 (3.9)</td>
<td>17 (77.3)</td>
</tr>
<tr>
<td>Non-participants with no cancer diagnosis ( N = 7542 )</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Control arm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically diagnosed cancer ( N = 4150 )</td>
<td>339 (8.2)</td>
<td>250 (73.8)</td>
</tr>
<tr>
<td>No cancer ( N = 44,151 )</td>
<td>1 (0.0)</td>
<td>1 (100.0)</td>
</tr>
</tbody>
</table>

**Table 2. Polygenic risk distribution among men with and without cancer in the Finnish screening trial**

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Scaled mean*</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men without prostate cancer ( N = 3878 )</td>
<td>−0.160</td>
<td>−0.198</td>
<td>0.397</td>
</tr>
<tr>
<td>Men with prostate cancer ( N = 1089 )</td>
<td>0.299</td>
<td>0.198</td>
<td>0.401</td>
</tr>
<tr>
<td>Men with screen-detected cancer ( N = 579 )</td>
<td>0.272</td>
<td>0.172</td>
<td>0.394</td>
</tr>
<tr>
<td>Men with clinically detected cancer ( N = 510 )</td>
<td>0.329</td>
<td>0.229</td>
<td>0.408</td>
</tr>
</tbody>
</table>

*By setting the mean polygenic relative risk in the population equal to unity.

Polygenic risk score is based on the known 66 prostate cancer susceptibility loci.

Overall, higher polygenic risk was associated with significantly increased odds of Gleason score \( \geq 7 \) tumours (odds ratio \( = 1.36, 95\%\) CI 0.85-2.16). The baseline incidence rate of prostate cancer in the control group was 6.17 cases per 1000 person-years (4150 cases/672 610 person-years from time of randomisation to censoring date). The estimated baseline incidence rates of prostate cancer were 2.47 and 9.90 cases per 1000 person-years in the lower and higher risk groups, respectively. The likelihood for the expected incidence rate of interval cancers was maximised for sensitivity of 0.55 (95% CI 0.45-0.65) and \( \lambda \) of 0.16 (95% CI 0.12-0.24) (Table 4).

Given these parameters, the expected number of screen-detected non-overdiagnosed cancers after three rounds of screening would be 950. As such 42% (95% CI 37-52; 696 out of 1646) of the observed screen-detected cancers would likely be overdiagnosed (Table 5).

The lower risk group would account for 50% of the screening episodes (\( N = 26\,186 \)) in the trial and almost 26% of the observed screen-detected cancers (\( N = 453 \)). A baseline incidence of 0.00247, \( S \) of 0.55 and \( \lambda \) of 0.16, the expected number of non-overdiagnosed cancers would be 191. Hence, 58% (95% CI 54-65; 262 out of 453) of the screen-detected cancers in the lower PRS group would likely be overdiagnosed.

The higher risk group would account for almost 50% of the screening episodes (\( N = 25\,957 \)) in the trial and almost 74% of the observed screen-detected cancers (\( N = 1193 \)). Using baseline incidence rate of 0.00090, \( S \) of 0.55 and \( \lambda \) of 0.16, the expected number of non-overdiagnosed cancers would be 756. Correspondingly, 37% (95% CI 31-47; 437 out of 1193) of the screen-detected cancers would likely be overdiagnosed.

At 13 years of follow-up, the overall overdiagnosed cases per 1000 men screened were 29, with 22 and 37 in the lower and higher polygenic risk groups, respectively.

Targeting screening to men in the higher risk group would miss 191 non-overdiagnosed cancers, while avoiding 262 overdiagnosed cancers. Targeted screening would reduce the overall cases overdiagnosed in the population from 29 (696 out of 23 771) to 18 (437 out of 23 771) per 1000 men.

In a sensitivity analysis, after excluding 9129 from the control group who had PSA test in the first 4 years and the expected subsequent 946 cancer diagnoses, the baseline incidence rate of stage and Gleason score, there was no statistically significant association between polygenic risk group and PSA categories (odds ratio = 1.35, 95% CI 0.89-2.04). Among the screen-detected cancers, there was statistically significant association between polygenic risk group and stage (\( P = 0.046 \)) and Gleason score categories (\( P = 0.005 \)). However, similar association was not seen among the clinically diagnosed cancers (Table 3).

Overdiagnosis for stage and Gleason score would likely be overdiagnosed.
prostate cancer in the control group was 5.87 cases per 1000 person-years (3204 cases/545 148 person-years from time of randomisation to censoring date). With baseline incidence rate of 0.00587, the $R$ and $l$ were derived as 0.52 and 0.16, respectively.

With these parameters, overall overdiagnosis was estimated as 37%, with 62% in the lower risk group and 37% in the higher risk group. This study, based on the Finnish prostate cancer screening trial with three rounds of screening, 31 700 screening episodes would detect 1000 cancers in these men, of which 577 would likely be non-overdiagnosed and 423 overdiagnosed. A polygenic risk-stratified screening programme would involve polygenic profiling of all men for risk stratification. Then the screening test, the PSA, would be offered to the strata of men above a certain polygenic risk threshold. As such a subset of men are offered PSA screening. Targeting screening to men in the higher polygenic risk group is estimated to reduce screening episodes by half while detecting 80% of the non-overdiagnosed cancers and reducing overdiagnosed cancers by 38% at a cost of missing 20% of the non-overdiagnosed cancers. That is, for every non-overdiagnosed cancer not detected through screening, almost two (37/20) overdiagnosed cases could be avoided.

We have reported similar inverse association between quartiles of polygenic risk and overdiagnosis using different analysis approach and using data from the UK on prevalence screening and incident cancers only (Pashayan et al, 2015). However, the study was limited by taking MST and test sensitivity values from different sources. In this study, having randomised screening trial
data with information on interval cancers, we estimated simulta-
neously the MST and episode sensitivity for non-overdiagnosed
cancers and from them derived the probability of overdiagnosis in
the Finnish trial setting. This enhances the validity of our results. We
do acknowledge, however, that the present results rely on a number
of assumptions, and that they remain subject to considerable
uncertainty. There is a need for continued development of rigorous
methods of estimation of overdiagnosis, including reliable confidence
interval estimation and for further data on screened and unscreened
populations with polygenic risk measured.

Although the proportion of screen-detected cancers that are
likely to be overdiagnosed decreased with polygenic risk, the
absolute rate of overdiagnosis increased with polygenic risk. This is
because majority of the cancers (74%) occurred in the higher risk
group. Although screening was estimated to result in 67% more
overdiagnosed cancers in the higher compared with the lower risk
group (437 vs 262), it also resulted in almost 300% more non-
overdiagnosed cancers in the higher risk group (756 vs 191). Thus,
overdiagnosis in the higher risk group is estimated to be
substantially smaller as a proportion of screen-detected cancers,
and would be expected to be correspondingly smaller in proportion
to prostate cancer deaths avoided.

We have used the maximum likelihood method to estimate
MST of 6.2 years and episode sensitivity of 55%. All estimates of
MST and sensitivity are subject to both sampling variation and
uncertainty due to other sources such as the distributional
assumptions involved. Our estimates are within the 95% CI of
previously reported estimates. Wu et al (2012) using multistate
modelling with the same Finnish screening trial data have reported
MST of 7.7 (95% CI 6.0-10.7) years and episode sensitivity of 43%
(95% CI 35-51) for the first screening round and 60% (95% CI 48-72)
for the second round. Our estimate of overdiagnosis of 42% is in line
with the estimates from the ERSPC (Draisma et al, 2003). Our
analysis indicates that 2.9% of men screened with three rounds of
screen are likely to be overdiagnosed. This estimate is comparable
to that of Wu et al (2012) of 3.4% (95% CI 2.1-5.7). These figures are
also consistent with other studies (Etzioni et al, 2002; Telesca et al,

It is of interest to know whether the natural history of the cancer
varies by genetic risk. However, the relatively small number of
cases, particularly in the lower polygenic risk group, limited
precision of the sensitivity and MST estimates by polygenic risk
group. As the majority of the cancers were in the higher polygenic
risk group, then the estimated MST and sensitivity are likely to
reflect primarily those of that population. Preliminary analysis
suggests similar episode sensitivity and longer MST in the lower
polygenic risk group. MST varying by polygenic risk is plausible
given the observed association between Gleason score and PRS.
With longer sojourn time, we would expect higher overdiagnosis
(Draisma et al, 2009) in the lower risk group. Risk groups with
longer MST may be offered less-frequent screening. As such
studying variation of MST with PRS is important for designing
risk-tailored screening.

The subsample of men with genotyping data and clinically
diagnosed cancer had less-aggressive and less-advanced cancers
than the remaining participants diagnosed clinically. Less-aggres-
sive cancers were associated with lower PRS. If our subsample had
more aggressive cancers, then the proportion of interval cancers
and baseline incidence rate in the higher risk group would have
been larger, resulting in even lower estimate of overdiagnosis in the
higher risk group.

Also, a sensitivity analysis accounting for some of the effect of
contamination yielded almost similar results.

In this study, we have used only polygenic risk profile for
stratification. Further research is needed to study the benefits, the
harms, and cost-effectiveness of stratifying the population into
several risk strata based on polygenic risk combined with other risk
factors, such as age, family history, and baseline PSA (Loeb, 2012;
Roobol and Carlsson, 2013), and offering screening differentially
different starting age, inter-screening interval, and screening
modality) to each population stratum.

In summary, polygenic risk-stratified screening for prostate
cancer could reduce the proportion of cancers overdiagnosed.
Targeting screening to men at higher polygenic risk could improve
the benefit to harm balance of screening.

Table 5. Proportion of screen-detected cancers which are likely to be overdiagnosed by polygenic risk

<table>
<thead>
<tr>
<th>Screening round</th>
<th>No. of screening episodes</th>
<th>No. of screen-detected cancer</th>
<th>Expected no. of non-overdiagnosed screen-detected cancer</th>
<th>Per cent (%) overdiagnosis (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening round 1</td>
<td>23 771</td>
<td>686</td>
<td>504</td>
<td>42 (37-52)</td>
</tr>
<tr>
<td>Screening round 2</td>
<td>18 044</td>
<td>596</td>
<td>272</td>
<td></td>
</tr>
<tr>
<td>Screening round 3</td>
<td>10 328</td>
<td>364</td>
<td>173</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>52 143</td>
<td>1646</td>
<td>949</td>
<td></td>
</tr>
<tr>
<td>PRS risk groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower risk group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening round 1</td>
<td>11 938</td>
<td>167</td>
<td>101</td>
<td></td>
</tr>
<tr>
<td>Screening round 2</td>
<td>9062</td>
<td>178</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Screening round 3</td>
<td>5187</td>
<td>108</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>26 186</td>
<td>453</td>
<td>191</td>
<td>58 (54-65)</td>
</tr>
<tr>
<td>Higher risk group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening round 1</td>
<td>11 833</td>
<td>519</td>
<td>402</td>
<td></td>
</tr>
<tr>
<td>Screening round 2</td>
<td>8982</td>
<td>418</td>
<td>217</td>
<td></td>
</tr>
<tr>
<td>Screening round 3</td>
<td>5141</td>
<td>256</td>
<td>139</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>25 957</td>
<td>1193</td>
<td>758</td>
<td>37 (31-47)</td>
</tr>
</tbody>
</table>

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

NP, PDP, and SD contributed to the conception of the study. SD designed the study, NP and SD contributed to the analysis, and NP, PDP, SD, and AA contributed to the interpretation of the findings, and NP drafted the manuscript. AA and TT are the principal investigators of the Finnish Prostate Cancer Screening Trial. JS, PH, JT, and RE contributed in generating and providing the genotyping data. KT and LM contributed in providing the trial data. PDP, JS, KT, TT, LM, PH, JT, RE, SWD, and AA contributed in revising the manuscript. All authors have seen and approved the submitted manuscript. NP had full access to all of the data in the study and takes responsibility for the integrity and accuracy of the submitted manuscript. PDP, JS, KT, TT, LM, PH, JT, RE, SWD, and AA contributed in genotyping data. KT and LM contributed in providing the trial data. PDP, JS, KT, TT, LM, PH, JT, RE, SWD, and AA contributed in revising the manuscript. All authors have seen and approved the submitted manuscript. NP had full access to all of the data in the study and takes responsibility for the integrity and accuracy of the submitted manuscript.

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