

An important step towards smarter screening for prostate cancer

The WHO reminds us that screening starts with a 'rough sorting process', to identify those at higher risk of the target condition, followed by a diagnostic test, to determine whether the condition is present¹. Nordstrom and colleagues are to be congratulated on their prostate cancer screening study, using a paired design for novel approaches at the first sort and then randomisation between standard biopsy and an MRI-first arm at the diagnostic test stage².

The European Randomised Screening for Prostate Cancer (ERSPC) is the only screening study to have shown a prostate cancer mortality reduction, with a 20% reduction at 16 year follow up³. However, this comes at a cost of significant overdiagnosis, and subsequent overtreatment, which have been a major barrier to adoption of formal prostate cancer screening. The ERSPC used digital rectal examination and the prostate specific antigen (PSA) blood test as the 'sorting' tests for men deemed at risk due to age, with standard transrectal biopsy as the diagnostic test for men who tested positive either on DRE or with a PSA of ≥ 3 ng/ml.

Nordstrom and colleagues have used a more complex initial first test, the Stockholm 3 risk calculator (STHLM3), which incorporates age, previous biopsy history, PSA derivatives and polygenic risk score based on a single nucleotide protein (SNP), and compared it to a PSA threshold of ≥ 3 ng/ml, with the STHLM3 showing an AUC of 0.76 for clinically significant cancer compared to 0.6 for PSA alone in this study. It is interesting that DRE has been omitted entirely in this study, and helpful as we progress towards a modern screening approach. Men were then randomised in a 2:3 manner to standard transrectal biopsy or MRI, with targeted and standard biopsy for any men with an MRI score of 3-5.

Eklund has recently published the findings from the same study, showing that MRI +/- targeted biopsy in this setting, when men are selected by a PSA threshold of ≥ 3 ng/ml alone, is non-inferior in the detection of clinically significant disease to standard biopsy, whilst allowing 60% of men to avoid biopsy, and reducing over-detection of indolent disease from 12% to 4%⁴. This finding in a screening population complements the PRECISION finding that MRI +/- targeted biopsy is superior to standard biopsy in a clinically selected population, where background risk and mean PSA are higher than in a screening population⁵.

Nordstrom & colleagues have demonstrated in this paper that there is equivalent detection of clinically significant cancer for an STHLM3 threshold of 0.15, compared to PSA ≥ 3 ng/ml, whilst reducing the need for MRI by one third, and biopsy by 8%. The novel paired sorting test, with minimal additional patient burden, and randomised diagnostic test allows assessment of both strategies. The economic impact of novel screening and diagnostic tools must be addressed. A recent analysis showed that compared to age based, biopsy first screening (such as in ERSPC), a risk stratified MRI first strategy would not only result in fewer prostate cancer deaths, fewer biopsies and fewer overdiagnoses, but also be cost effective⁶.

A number of factors will contribute to the success or otherwise of a screening programme, including uptake of the invitation, test performance of both screening and diagnostic tools, and the ability of treatment to reduce mortality.

This study showed 26% uptake of the screening invitation, compared to 32% uptake of the ERSPC invitation in the Netherlands at the outset, increasing to 42% over time⁷. Formal national screening programmes aim for uptake of 70-80% uptake. The authors do not report the uptake of the invitation across different parts of the community. However, current data shows that black men, who are at increased risk of prostate cancer, may be less likely to take up an invitation for prostate cancer screening⁸. A combination of interventions may be appropriate to increase uptake⁹, and the potential increase in acceptability in removing the need for digital rectal examination seems likely to contribute to a willingness to be screened across many communities.

A further challenge is the implementation of high quality MRI for all, as this is significantly more challenging than standard TRUS biopsy¹⁰. Implementation requires a co-ordinated approach across a number of departments including imaging, urology and histopathology, and may include a formal quality assurance and quality control programme, with accreditation by professional bodies.

This study has shown advantages over the traditional PSA and standard biopsy approach, in both the initial 'sort' test and the diagnostic test. Further work will be needed to assess the generalisability and cost-effectiveness of this approach.

Word count 750/750

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