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NEWS AND VIEWS

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Modern prostate cancer diagnostics reduce overdiagnosis – will they open up for population-based screening?

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Clinical context: Population-based screening for prostate cancer with PSA tests and systematic prostate biopsies reduces cancer-specific mortality as much as screening for breast and colorectal cancer, but results in more harms in form of overdiagnosis and overtreatment. The key to open the door for prostate cancer screening is therefore better diagnostic methods that more specifically detect potentially lethal cancer. Much research has been invested over the past decades to find this key. The research has produced solid evidence that various biomarkers and MRI with targeted biopsies reduce the proportions of men that need a biopsy and are diagnosed with Gleason score (GS) 6 cancer, but before summer 2021 there were no results from prospective, population-based trials using MRI and few from studies combining MRI and biomarkers in screening settings.

News: The population-based Stockholm3-MRI trial invited 49,000 men aged 50–74 years [1,2], of whom close to 13,000 accepted to participate and had a PSA test. Men with PSA $\geq$1.5 ng/ml received a Stockholm3 test using the same tube of blood. Stockholm3 is a combination of serum biomarkers, a genetic risk score, and data on family history and previous prostate biopsy collected online at inclusion. All men with PSA $\geq$3.0 ng/ml or a Stockholm3 test result indicating $\geq$ 11% probability of detecting a 'clinically significant' (GS $\geq$7) cancer on systematic biopsy (based on a previous study [3]) were randomly allocated 2:3 to either systematic biopsy (921 men) or biparametric prostate MRI (1372 men) followed by both targeted and systematic biopsies if the MRI showed a suspicious lesion (PI-RADS 3–5). Men with unsuspicious MRI had no biopsy, unless the Stockholm3 test indicated $\geq$25% risk of GS $\geq$7 cancer.

The results from using MRI only in men with PSA $\geq$ 3.0 ng/ml were reported separately [1]. The MRI pathway detected as many GS $\geq$7 cancers (21 versus 18%), but fewer GS 6 cancers (4% versus 12%) and saved half of the men from having a biopsy, compared with systematic biopsies for all men with PSA $\geq$3.0 ng/ml. Using a 15% cut-off of the Stockholm3 test in combination with MRI-targeted biopsies, by design detected GS $\geq$7 cancers in as many men as using PSA $\geq$3.0 ng/ml and MRI-targeted biopsies (2.5% of the initially tested men), but with 36% fewer MRI scans. The number of biopsy procedures and men diagnosed with GS 6 cancer were similar [2]. Lowering the Stockholm3 cut-off to 11% would detect more GS $\geq$7 cancers (3.0%), but at the expense of higher numbers of unnecessary biopsy procedures and diagnoses of GS 6 cancers. Both Stockholm3/MRI pathways reduced post-biopsy infections compared with standard biopsies for men with PSA $\geq$ 3.0 ng/ml.

Views: The Stockholm3-MRI trial is excellently designed and carried out, and we congratulate the investigators on their accomplishment. These reports add valuable information on the diagnostic outcomes of using MRI and targeted biopsies with or without a blood biomarker panel in a population-based screening setting. Without doubt, modern prostate cancer diagnostics reduce harms from unnecessary biopsy procedures and overdiagnosis of GS 6 cancers. We believe that a key opening up for prostate cancer screening has been found, but that it needs some polishing before it fits the key hole:

First, the 15% Stockholm3 cut-off should be externally validated and higher PSA cut-offs than 1.5 ng/ml investigated. As mortality reduction from population-based prostate cancer screening may be limited to men with PSA $\geq$2.0 ng/ml [4], the use of the Stockholm3 test only in men with PSA $\geq$ 2.0 ng/ml could reduce the number of men having the test by approximately 30% [5] and thereby decrease costs of a population-based screening programme without compromising its efficacy. Moreover, it is desirable that future studies achieve higher participation rates; the low (26%) participation rate and lack of information about non-participants make it impossible to rule out selection biases.

Second, PSA density was not included in the trial's MRI pathway. It is reasonable to assume that using PSA density for the selecting men without a strongly suspicious tumour on MRI (i.e. those with PI-RADS 1–3) for biopsy would result in diagnostic improvements for the MRI only pathway [6].

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Third, MRI and the Stockholm3 test need to be evaluated for repeated testing to enable planning of the resource allocation for a future screening programme. Results from repeated screening rounds are expected from the MRI based Göteborg-2 trial in late 2022 and from the Finnish ProScreen trial, in which the 4Kscore test is combined with MRI, a couple of years later [7,8].

Fourth, the genetic part of the Stockholm3 test mandates ethical and medicolegal considerations [9].

Finally, although the Stockholm3-MRI trial shows that modern diagnostics reduce overdiagnosis it does not show by *how much*. Some men diagnosed with 'clinically significant cancer' in the trial would have died from other causes than their prostate cancer even if it had been left undiagnosed and untreated. The proportion of overdiagnosed GS $3+4=7$ cancers is probably substantial [10]. It takes advanced modelling, using data from repeated testing, to estimate how much the use of MRI alone and in different combinations with PSA density, the Stockholm3 test or other biomarkers would reduce overdiagnosis in a long-term screening programme. Fortunately, the research community is buzzing with activity, so there is a good chance that the key will fit the keyhole within a few years.

Disclosure statement

Hans Lilja is named on patents on assays for intact PSA and patents on a statistical method to detect prostate cancer (4KScore test) licensed to Arctic Partners that is sublicensed to and commercialized by OPKO Health. Hans Lilja receives royalties from sales of this test, and has stock in OPKO Health, Arctic Partners, Diaprost AB, and Acousort AB. No potential conflict of interest was reported by Ola Bratt.

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