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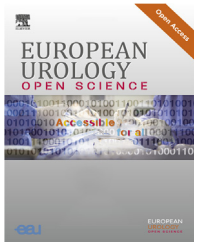

European Association of Urology

Brief Correspondence

Implications of the European Association of Urology Recommended Risk Assessment Algorithm for Early Prostate Cancer Detection

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Abstract

The 2021 European Association of Urology recommendations for early prostate cancer detection included a risk-based algorithm. Risk assessment methods are proposed to prevent excessive use of prostate magnetic resonance imaging (MRI) and biopsy, simultaneously reducing overdiagnosis and overtreatment. However, the clinical implications of sequential use of risk assessment tests have not yet been properly assessed. We provide an appraisal of the recommended algorithm and evaluate its outcomes in a contemporary prospective study population of biopsy-naïve men. To increase the effectiveness in cases of limited MRI capacity, we show that use of the Rotterdam Prostate Cancer Risk Calculator-3 for pre-MRI risk stratification could avoid more than one-third of MRI examinations. After prostate MRI, use of either the Prostate Imaging-Reporting and Data System (PI-RADS) score or a risk model including MRI outcome as a variable could avoid six out of ten prostate biopsies while maintaining high sensitivity. However, implementation in health care systems requires due consideration of the access to and quality of diagnostic resources, as well as cost-effectiveness.

Patient summary: We evaluated the European Association of Urology risk-based strategy for early prostate cancer detection. Risk assessment before magnetic resonance imaging (MRI) using a risk calculator or prostate-specific antigen (PSA) density could reduce MRI demands and overdiagnosis of insignificant cancers. Risk assessment using prostate MRI results could avoid 60% of prostate biopsies while maintaining prostate cancer detection rates.

The European Association of Urology (EAU) recently published its current position and recommendations on prostate-specific antigen (PSA) testing [1]. On the basis of the literature and expert opinion, a risk-based algorithm for early detection of prostate cancer (PCa) was proposed. The guideline recommends stratifying men with PSA $\geq$3 ng/ml as either "low risk", for whom magnetic resonance imaging (MRI) can be avoided, or "intermediate and high risk", for whom prostate MRI should be performed as a basis for further diagnostic decisions. Strategies must be developed to use health care resources efficiently and to reduce unnecessary morbidity, anxiety, and costs of diagnostics. However, any paradigm shift inevitably leads to a paucity of research data. As a result, there is still debate regarding which men can safely avoid an initial MRI but are subjected to clinical follow-up, and which men must undergo an immediate MRI. The authors proposed four methods for risk assessment: (1) family history; (2) PSA velocity; (3) PSA density; and (4) risk calculators. It must be stressed that the availability and quality of prostate

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MRI in each situation should be considered when using these pre-MRI risk assessment tools. We discuss in brief the proposed risk assessment methods including MRI and assess potential outcomes in a contemporary population.

First, regarding family history, it would help to understand how a "positive" family history is defined and how it relates to certain risk classifications. Second, we would appreciate advice on how to use PSA velocity for this purpose. How does this relate to the acknowledgment in the 2021 EAU guideline on PCa that PSA velocity (or doubling time) provides limited to no additional diagnostic information compared to PSA alone [2]?

PSA density has proven to be a valuable predictor of clinically significant PCa (csPCa; grade group ≥2, although this definition is a topic of ongoing debate) either alone or combined with MRI findings or incorporated into risk models [3–5]. Nonetheless, most studies show the impact of PSA density on the potential number of csPCa cases detected and biopsies avoided rather than its use for pre-MRI risk stratification.

Various risk calculators have been developed to improve the discrimination of csPCa and to guide decision-making regarding biopsy [4,6–8]. To date, only a few articles have shown the role of these risk calculators as a stratification tool before MRI. Alberts et al. [9] determined their value after a previous negative biopsy, while Mannaerts and colleagues [10] retrospectively showed the role of the Rotterdam Prostate Cancer Risk Calculator (RPCRC) in 200 biopsy-naïve men. Upfront stratification using a cutoff risk of ≥20% for PCa and/or csPCa risk of ≥5% would have avoided 73/200 (37%) MRI scans at the cost of missing 4/67 (5.9%) csPCa cases. We assume that this is the basis for the EAU recommendation that approximately 35% of men are at low risk and can thus avoid MRI. However, one should be aware that a sequence of tests as proposed in the algorithm results in the total sum of missed csPCa cases at each step. Determining the appropriate clinical risk threshold should be based on multiple factors, such as (expected) csPCa prevalence, procedural costs, MRI availability and expertise, and the accepted ratio of excessive prostate MRI/biopsies performed versus the number of csPCa cases detected. In addition, the inclusion of other tools such as blood and urinary molecular markers has shown promising results and may improve risk stratification before MRI [11–13].

Following pre-MRI risk stratification, men with intermediate or high risk undergo MRI. According to the EAU recommendation, 54% of men with intermediate or high risk will have Prostate Imaging-Reporting and Data System (PI-RADS) scores of 1–2 [1,14]. Similar rates (49–59%) have been reported by expert centers, but it should be noted that these percentages were from (screening) populations not yet stratified using pre-MRI risk assessment tools [13,15,16]. A recent Cochrane systematic review that also included centers with less prostate MRI expertise showed that the group of biopsy-naïve men with a clinical suspicion of PCa had a markedly lower PI-RADS 1–2 assessment rate (33%) [17]; the prevalence of csPCa among studies included in the systematic review was 30%. After pre-MRI stratification, this would lead to a csPCa prevalence of 45% in the intermediate/high risk group when the RPCRC threshold of Mannaerts et al. is applied [10,17]. Despite the excellent accuracy of prostate MRI in excluding csPCa, the rate of 54% with PI-RADS 1–2 suggested by Van Poppel and colleagues [1] is likely to be an overestimation because it would require an (improbable) near-perfect MRI diagnostic performance, as 45% of men have csPCa and should therefore all be assigned PI-RADS scores of 3–5. Furthermore, in situations involving lower csPCa prevalence (eg, in PCa screening) the specificity needs to be considerably higher than reported in the current literature [17]. How likely is it that novel risk calculators with integrated imaging parameters will close this gap [6,18]? There is overlap between variables in pre-MRI and post-MRI risk models, and sequential use could be associated with high correlation.

Figure 1 shows RPCRC-3 and PSA density results for pre-MRI risk assessment in a contemporary population assessed within a multicenter prospective trial [16]. A total of 613 biopsy-naïve men with PSA ≥3 ng/ml who underwent prebiopsy MRI, prostate biopsy (12-core systematic biopsy, combined with targeted biopsy in cases with a PI-RADS score of 3–5) and had complete data available for the risk model evaluations were eligible [16]. Using the RPCRC-3 cutoff suggested by Mannaerts et al. [10] could have avoided prostate MRI in 4/10 men, missing csPCa in 4% of cases. If prostate MRI is only performed when the predicted risk is above this threshold, this would result in a biopsy avoidance rate of 60% (41% of the low risk group and 19% of the group with PI-RADS 1–2), missing csPCa in 5% of cases (4% low risk and 1% PI-RADS 1–2). For PSA density, a threshold of ≥0.10 ng/ml/ml resulted in a lower number of MRI scans avoided in comparison to use of the RPCRC-3 (34% vs 41%); however, after MRI the csPCa detection and biopsy avoidance rates were equal.

Furthermore, we assessed the performance of a post-MRI risk calculator by Alberts and colleagues [6] who included PI-RADS score as a variable. Figure 1 shows that this post-MRI risk calculator has biopsy avoidance and csPCa detection rates comparable to those using the PI-RADS score alone. A plausible reason for the limited added value of the post-MRI risk calculator could be the high level of MRI expertise in our study. Supplementary Figure 1 shows the outcomes for a PSA density threshold of ≥0.12 ng/ml/ml for pre-MRI risk assessment and for different post-MRI risk calculator cutoffs.

To conclude, the expert EAU group has made enormous efforts to develop an algorithm tailored to optimize the balance between the benefits and harms of early PCa detection. To improve the use of scarce MRI caacity, pre-MRI risk assessment using either a risk calculator or PSA density could avoid over one-third of examinations. However, we

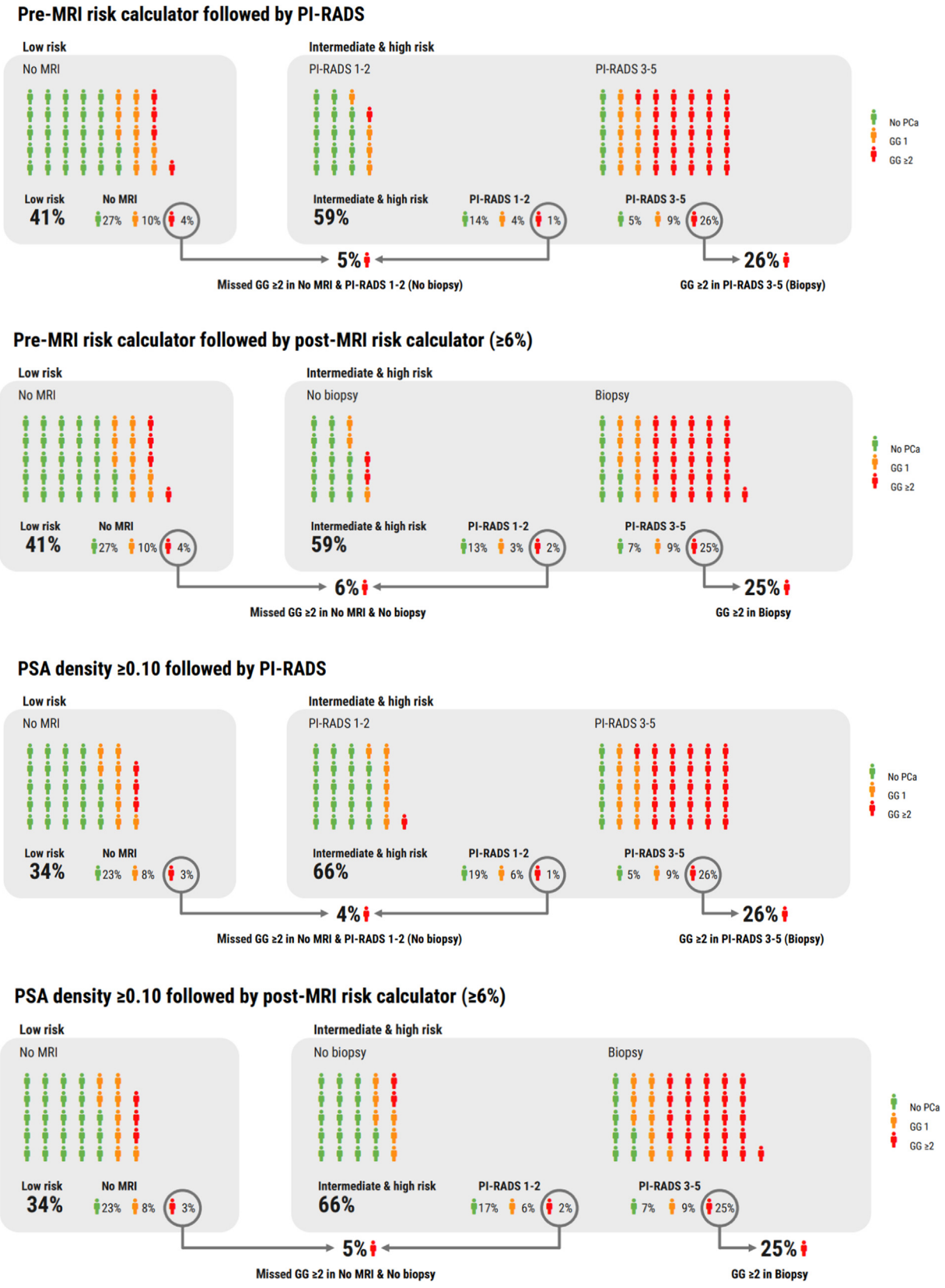

Fig. 1 – Outcomes for the European Association of Urology risk-adapted algorithm for early prostate cancer detection applied to a contemporary cohort. Pre-MRI risk calculator (RPCRC-3): cutoff value similar to Mannaerts et al. [10]: risk of any prostate cancer of ≥20% and/or a risk of clinically significant prostate cancer of ≥5%. Post-MRI risk calculator (Alberts et al. [6]): MRI-incorporated risk calculator cutoff of ≥6% for clinically significant prostate cancer; outcomes for other thresholds are shown in Supplementary Figure 1 [18]. Total detection rates of grade group 1 (*n* = 142; 23% of 613) and grade group ≥2 (*n* = 186; 30% of 613) were determined via 12-core systematic transrectal ultrasound biopsy in all men, with additional in-bore MRI-targeted biopsy in cases of PI-RADS scores of 3–5. Differences in percentages reported are due to rounding. GG = grade group; MRI = magnetic resonance imaging; PI-RADS = Prostate Imaging-Reporting and Data System; PSA = prostate-specific antigen; RPCRC = Rotterdam Prostate Cancer Risk Calculator.

are ambiguous about how to use family history and PSA velocity for this purpose. If only men with intermediate and high risk undergo prostate MRI, prostate biopsies could be avoided in ~60% of men while maintaining a high sensitivity. Nevertheless, before implementation in health care systems, access to and the quality of diagnostic resources, as well as cost-effectiveness, should be taken into account.

Author contributions: Bas Israël had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Israël, Hannink, Barentsz.
Acquisition of data: Israël, van der Leest.
Analysis and interpretation of data: Israël, Hannink, Barentsz, van der Leest.
Drafting of the manuscript: Israël, Hannink.
Critical revision of the manuscript for important intellectual content: Israël, Hannink, Barentsz, van der Leest.
Statistical analysis: Israël, Hannink.
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Supervision: Barentsz.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2022.06.006.

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