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Challenges in adopting level I evidence for multiparametric magnetic resonance imaging as a biomarker for prostate cancer screening

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PRECISION is the first randomized trial to demonstrate the value of an adjunctive test for men with elevated prostate-specific antigen (PSA). Multiparametric magnetic resonance imaging (mp-MRI) and MRI-ultrasound fusion targeted biopsy of suspicious lesions was reported to improve both the sensitivity and specificity of PSA, with fewer biopsies conducted but more high-grade cancers diagnosed in patients randomized to MRI compared to standard systematic prostate biopsy[1].

We tend to think of randomized trials as providing the best data - “level I evidence” – to inform clinical practice, and that the next step after publication of a randomized trial is to consider how to implement the results. However, before widespread adoption of mp-MRI as an adjunctive test for men with elevated PSA, we need to address questions of whether PRECISION provides sufficient evidence to support routine use of mp-MRI, as well as consider the practical implications of widespread mp-MRI implementation.

Limitations of the evidence.

PRECISION does provide excellent data on mp-MRI, but several important questions remain unanswered. One of the key findings, and a purported advantage of mp-MRI, is that 28% of men in the mp-MRI group avoided biopsy, reducing the risk of biopsy complications such as sepsis, as well as lowering overdiagnosis of indolent disease. But as the PRECISION authors acknowledge, there is no long-term follow-up for these men, and estimates from the literature suggest that 12 – 33% of those not biopsied harbor high-grade disease[2]. The PRECISION authors highlight the 5.5% absolute risk benefit of MRI-targeted biopsy for detecting high grade disease. Their argument is that although mp-MRI may indeed lead to some missed high-grade tumors in patients with false negative imaging, this is more than made up for by the extra high-grade tumors that would be missed by systematic biopsy, but that are identified by targeting MRI lesions. Yet this assumes the oncologic equivalence of high-grade tumors not visible on mp-MRI and high-grade tumors missed by systematic

biopsy. There is good evidence that the latter are relatively indolent. When Danish cancer registry data was examined for long-term outcomes in patients with a negative biopsy, the cumulative incidence of prostate-cancer specific death after 15 years was 0.7% in patients with PSA <10 ng/ml[3], by far the most common presentation in PRECISION and in urologic practice in the US. This suggests that high-grade cancers missed by systematic biopsy but targeted by mp-MRI are unlikely to be aggressive. On the other hand, the oncologic relevance of high-grade tumors that do not appear on mp-MRI is yet to be fully characterized. Hence we require further data on the relative aggressiveness of high-grade tumors found and missed by mp-MRI.

Practicalities of implementing mp-MRI.

Even were such evidence for mp-MRI to become available, there are several practical gaps that must be bridged before it could be implemented in routine practice. The first is cost. By 2020, US costs of prostate cancer care alone are projected to increase to \$16.3 billion [4]. Obtaining a mp-MRI for every man with an elevated PSA will sharply accelerate this increase. New Choice Health (www.newchoicehealth.com), an online marketplace whose mission is to increase price transparency, estimates the national mean cost of mp-MRI to be \$2,550. As there are approximately 1 to 1.2 million prostate biopsies performed annually in the US, widespread mp-MRI adoption prior to biopsy would contribute \$3 billion annually, that is, about 15% of the entire cost of managing prostate cancer would be related to a pre-diagnostic imaging test.

Beyond costs, the feasibility of performing a large volume of mp-MRI nationally must be considered. Although almost all academic centers perform prostate MRI, only 30% of community hospitals do so[5]. Furthermore, only 25% of hospitals perform more than 20 mp-MRI monthly, with significant heterogeneity in mp-MRI protocols [5]. Although the Prostate Imaging Reporting and Data System version 2 has consensus protocol guidelines, adherence varies.

The low volume of mp-MRI being performed at most institutions raises the issue of the learning curve. A comparison of initial and tertiary center mp-MRI findings revealed discordance in 54% of cases, with a significant improvement in both negative predictive value (0.89 vs. 0.72) and positive predictive value (0.61 vs. 0.28) on second-opinion interpretation by sub-specialist urologists at the tertiary centers[6]. Published negative and positive predictive values of mp-MRI, and results from studies such as PRECISION, are largely from tertiary centers with optimized MRI protocols and sub-specialist radiologists. Implementation of mp-MRI across the US would entail that many patients have images reviewed in community settings. Accordingly, the benefit-to-harm ratio of mp-MRI reported in the literature is likely to be highly attenuated in practice. Adding to this problem, a significant learning curve for MRI-targeted biopsy is also evident for urologists. In our experience as a referral center, MRI-ultrasound fusion software tracked differences between intended versus actual targeted biopsy core trajectories and demonstrated improvement from 6.7 to 0.6 mm ($p<0.01$) over 170 cases. Increasing the number of sub-specialized radiologists, providing additional training to radiologists and urologists at non-tertiary

centers and development of artificial intelligence applications are possible solutions, but are not ready for prime time and would require considerable resources to implement.

Our view is that practical implementation of mp-MRI needs to consider the wider context of tests that can help inform biopsy decision-making. Several blood markers are now available that can predict the risk of high-grade cancer in men with elevated PSA, including free-to-total PSA ratio, Prostate Health Index and the 4kScore [7]. Consider the two following workflows:

- A. Men undergoing prostate cancer screening in primary care who have an elevated PSA (e.g. PSA ≥ 3 ng/ml) have secondary blood markers evaluated, something which could be implemented at the clinical laboratory as a reflex test on the same blood sample. Patients found to be at low risk may continue future screening based on age, risk factors and shared decision-making. Men at higher risk are referred to a urologist, who can decide to biopsy immediately (if, for instance, a man is found to be at very high risk by the adjunctive blood test) or order an mp-MRI to help determine whether biopsy is indicated.
- B. Primary care physicians refer a patient with an elevated PSA directly to a urologist for mp-MRI. If the mp-MRI shows high risk (e.g. PIRADS 4 or 5 lesions), the patient undergoes an MRI-ultrasound targeted biopsy; otherwise, the patient has a second blood test with the decision for biopsy guided by blood markers.

The second paradigm closely resembles the PRECISION study, but the first paradigm will be more convenient and less anxiety-inducing to the patient, less costly to the healthcare system, and more practical to implement with currently available resources.

mp-MRI undoubtedly offers value in select clinical scenarios, such as for a man with a high PSA and negative systematic biopsy. An immediate impact of PRECISION will be to arm patients and providers with evidence to appeal health plan rejection of mp-MRI for elevated PSA. However, routine use of mp-MRI to evaluate every patient with an elevated PSA is neither justified by current evidence nor practical at this time.

Conflicts of Interest/Acknowledgments

SK: None

AV: AV is named on a patent for a statistical method to detect prostate cancer. The method has been commercialized by OPKO Health. AV receives royalties from sales of the test and has stock options in OPKO Health.

JH: Speakers bureau for Genomic Health.

References

- Kasivisvanathan V, et al., MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. *N Engl J Med*, 2018.
- Moldovan PC, et al., What Is the Negative Predictive Value of Multiparametric Magnetic Resonance Imaging in Excluding Prostate Cancer at Biopsy? A Systematic Review and Meta-analysis from the European Association of Urology Prostate Cancer Guidelines Panel. *Eur Urol*, 2017 72(2): p. 250–266. [PubMed: 28336078]

3. Klemann N, et al., Risk of prostate cancer diagnosis and mortality in men with a benign initial transrectal ultrasound-guided biopsy set: a population-based study. *The Lancet Oncology*, 2017 18(2): p. 221–229. [PubMed: 28094199]
4. Mariotto ABY, K. R; Shao Y; Feurer EJ; Brown ML, Projections of the cost of cancer care in the United States: 2010–2020. *J Natl Cancer Inst*, 2010 103(2): p. 117–128.
5. Leake JL, et al., Prostate MRI: access to and current practice of prostate MRI in the United States. *J Am Coll Radiol*, 2014 11(2): p. 156–60. [PubMed: 24389134]
6. Hansen NL, et al., Comparison of initial and tertiary centre second opinion reads of multiparametric magnetic resonance imaging of the prostate prior to repeat biopsy. *Eur Radiol*, 2017 27(6): p. 2259–2266. [PubMed: 27778089]
7. Vickers AJ, et al., The Memorial Sloan Kettering Cancer Center Recommendations for Prostate Cancer Screening. *Urology*, 2016 91: p. 12–8. [PubMed: 26850815]