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## Prostate Magnetic Resonance Imaging and Magnetic Resonance Imaging Targeted Biopsy in Patients with a Prior Negative Biopsy: A Consensus Statement by AUA and SAR

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## Abstract

**Purpose:** After an initial negative biopsy there is an ongoing need for strategies to improve patient selection for repeat biopsy as well as the diagnostic yield from repeat biopsies.

**Materials and Methods:** As a collaborative initiative of the AUA (American Urological Association) and SAR (Society of Abdominal Radiology) Prostate Cancer Disease Focused Panel, an expert panel of urologists and radiologists conducted a literature review and formed consensus statements regarding the role of prostate magnetic resonance imaging and magnetic resonance imaging targeted biopsy in patients with a negative biopsy, which are summarized in this review.

**Results:** The panel recognizes that many options exist for men with a previously negative biopsy. If a biopsy is recommended, prostate magnetic resonance imaging and subsequent magnetic resonance imaging targeted cores appear to facilitate the detection of clinically significant disease over standardized repeat biopsy. Thus, when high quality prostate magnetic resonance imaging is available, it should be strongly considered for any patient with a prior negative biopsy who has persistent clinical suspicion for prostate cancer and who is under evaluation for a possible repeat biopsy. The decision of whether to perform magnetic resonance imaging in this setting must also take into account the results of any other biomarkers and the cost of the examination, as well as the availability of high quality prostate magnetic resonance imaging interpretation. If magnetic resonance imaging is done, it should be performed, interpreted and reported in accordance with PI-RADS version 2 (v2) guidelines. Experience of the reporting radiologist and biopsy operator are required to achieve optimal results and practices integrating prostate magnetic resonance imaging into patient care are advised to implement quality assurance programs to monitor targeted biopsy results.

**Conclusions:** Patients receiving a PI-RADS assessment category of 3 to 5 warrant repeat biopsy with image guided targeting. While transrectal ultrasound guided magnetic resonance imaging fusion or in-bore magnetic resonance imaging targeting may be valuable for more reliable targeting, especially for lesions that are small or in difficult locations, in the absence of such targeting technologies cognitive (visual) targeting remains a reasonable approach in skilled hands. At least 2 targeted cores should be obtained from each magnetic resonance imaging defined target. Given the number of studies showing a proportion of missed clinically significant cancers by magnetic resonance imaging targeted cores, a case specific decision must be made whether to also perform concurrent systematic sampling. However, performing solely targeted biopsy should only be considered once quality assurance efforts have validated the performance of prostate magnetic resonance imaging interpretations with results consistent with the published literature. In patients with negative or low suspicion magnetic resonance imaging (PI-RADS assessment category of 1 or 2, respectively), other ancillary markers (ie PSA, PSAD, PSAV, PCA3, PHI, 4K) may be of value in identifying patients warranting repeat systematic biopsy, although further data are needed on this topic. If a repeat biopsy is deferred on the basis of magnetic resonance imaging findings,

then continued clinical and laboratory followup is advised and consideration should be given to incorporating repeat magnetic resonance imaging in this diagnostic surveillance regimen.

### Keywords

prostatic neoplasms; biopsy; magnetic resonance imaging; consensus

Prostate MRI has undergone substantial technological improvement during the last 10 years. Meanwhile, radiologists and urologists are gaining experience and training in prostate MRI, and uniform reporting standards are being established.<sup>1,2</sup> New technologies have been developed to facilitate the performance of biopsies targeting MRI defined lesions.<sup>3</sup> As a result, an increasing number of urological practices are incorporating prostate MRI into the routine care of selected patients with a prior negative biopsy. Prostate MRI is being used to identify patients with a prior negative biopsy who warrant repeat biopsy by identifying regions of interest to target, and to direct biopsies to these suspicious areas under image guidance. A growing body of literature demonstrates the value of MRI targeted biopsy in the repeat biopsy setting.

A collaborative expert panel consisting of radiologists and urologists was convened to evaluate the use of prostate MRI and MRI targeted biopsy in patients with a prior negative biopsy. The full consensus statement is available online (<http://www.auanet.org/common/pdf/education/clinicalguidance/Consensus-Statement-Prostate-MRI-and-MRI-Targeted-Biopsy.pdf>) and incorporates a detailed literature review on which the panel recommendations are based. This article provides an abbreviated summary of the complete consensus statement, focusing on quality assurance and the specific recommendations.

## QUALITY ASSURANCE OF PROSTATE MRI INTERPRETATION

Marked variation not only in image quality, but also in radiologists' performance in examination interpretation, is a primary barrier to the widespread clinical adoption of prostate MRI. Currently there is no standardization for image quality and examination quality may vary across centers using the same MRI system based on the achieved level of scan optimization. Moreover the interpretation of prostate MRI is inherently challenging as a result of a spectrum of diagnostic pitfalls that may result in a false-positive or false-negative reading. Indeed, the literature has demonstrated improved performance in prostate MRI interpretation among more experienced radiologists.<sup>4-6</sup> Thus, to date, the implementation of prostate MRI and MRI targeted biopsy has remained most heavily concentrated in major academic centers that have developed the necessary radiological experience and expertise to provide accurate MRI interpretations. For prostate MRI to be widely adopted, community radiologists will also need to become trained and experienced.

As of this writing there is no formal mechanism for radiologists to become certified in prostate MRI interpretation, nor an established number of examinations that must be interpreted for radiologists to achieve sufficient experience. However, various educational opportunities are available to assist radiologists in achieving the appropriate level of interpretive skill.<sup>7</sup> Many hands-on courses and symposia are routinely offered that combine didactic lectures with interactive workshops and supervised case review at workstations.<sup>8</sup> In

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addition, regular participation in a local multidisciplinary conference can facilitate dialogues among specialties that may improve the reporting patterns of radiologists. Perhaps most important, it is critical that interpreting radiologists participate in ongoing case review, comparing prospective interpretations with subsequent histological results from targeted biopsy and prostatectomy. Such urological and pathological feedback is needed to help the radiologist identify and correct systematic causes of false-positive and false-negative interpretations.

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The consensus statements in this article are contingent upon the availability of quality prostate MRI acquisition and interpretation by individuals with sufficient experience and skill in the area, as well as the experience of the operators in performing the MRI targeted biopsy. Provided with sufficient expertise in prostate MRI interpretation and MRI targeted biopsy, prostate MRI use can benefit the treatment of patients with a prior negative biopsy. Conversely, if expertise is lacking, the proposed clinical usefulness of prostate MRI is unlikely to be achieved, and misleading information and harmful consequences are possible. Thus, the authors entreat radiologists interpreting MRI to pursue routine quality assessments as well as education and other measures to improve the quality of their MRI interpretations. Practices seeking to adopt a comprehensive program of diagnostic MRI and MRI targeted prostate biopsy must actively engage in such quality assurance efforts to ensure sufficient accuracy, obtaining histological validation of their interpretations before broadly integrating prostate MRI into local practice.

## CONSENSUS STATEMENTS

### Consensus Statement on Detection of CS Cancer at Re-biopsy Using MRI Targeting

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Numerous studies report the CDR of CS disease on repeat biopsy using MRI targeting. Variation in CDR likely represents differing criteria for CS cancer, patient selection for MRI and MRI targeted biopsy, quality of imaging and targeting methodology. The CDR of CS cancer on MRI targeted biopsy in the re-biopsy setting ranges from 11% to 54%, although it ranges from 16% to 40% when restricting inclusion to studies that define CS cancer as Gleason score 7 or greater. Additionally, the data indicate the potential to increase CS cancer detection on repeat biopsy when comparing MRI targeted biopsies to standard systematic sampling alone.

### Consensus Statement on Patient Selection for Repeat MRI Directed Biopsies

The accumulated evidence suggests prostate MRI has value for detecting CS cancer in patients with a prior negative biopsy and a persistently elevated or increasing PSA, regardless of the number of prior negative standard biopsies.

### Background on MRI Targeted Biopsy Methods

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There are 3 major strategies for targeting MRI defined lesions in the repeat biopsy setting. The approach involving the least amount of advanced technology is cognitive targeting, which involves estimating the location of a lesion detected on MRI and mentally transferring the target to the TRUS image during TRUS guided biopsy without any technological

guidance. This approach does not require any additional hardware or software investment and can be applied in any clinical practice in which pre-biopsy MRI is available.

The obvious limitation of this approach is the lack of visual feedback regarding the accuracy of targeting the suspected cancerous lesion on MRI. The accuracy of this method is highly dependent on the operator's familiarity with prostate MRI, and ability to accurately and consistently correlate MRI targets to real-time ultrasound images with reasonable fidelity. The reliability of this approach is of particular concern for lesions that are small or anterior, or in locations otherwise difficult to target. Nevertheless, good results with cognitive biopsy have appeared in the literature.<sup>9-11</sup>

A second approach is to perform targeted biopsy while the patient is in the MRI gantry. With this technique magnetic resonance images can be obtained to confirm placement of the needle in the target. This approach offers the advantage of being the most direct targeting. However, the procedure is relatively time-consuming and labor-intensive, as well as potentially uncomfortable for the patient, who is often in the prone position during the extended procedure time (45 to 60 minutes for multiple targets). In addition, concurrent systematic biopsies are not usually obtained because of the time constraints of the in-bore procedure.

A third approach is real-time MRI/ultrasound fusion guided prostate biopsy. With this method a planning session is performed in advance of the biopsy procedure in which the boundaries of the prostate and the location of the target(s) are outlined on the magnetic resonance image using vendor specific segmentation software and needle tracking methods. The 3-dimensional prostate and target map are loaded into the fusion biopsy system before the biopsy. At the time of biopsy the MRI data are fused to the TRUS imaging data to align the MRI and TRUS prostate segmentations, and link their movements so the biopsy can be performed under TRUS but using MRI guidance.

Studies suggest reasonable registration accuracy of fusion algorithms with a registration error of approximately 3 mm.<sup>12-14</sup> MRI/ultrasound fusion biopsy offers several advantages. Those who perform TRUS biopsy are already familiar with the principal elements of the procedure. The procedure is only approximately 5 to 10 minutes longer than routine TRUS biopsy and can be incorporated into the existing clinical workflow. In addition, obtaining concurrent systematic cores, if desired, can be readily performed in the same session. A potential disadvantage of this method is the possibility of co-registration error.

There are numerous studies demonstrating the usefulness of the detection of CS cancer using the 3 approaches of cognitive targeting,<sup>9-11</sup> in-bore targeting<sup>15-18</sup> and fusion targeting.<sup>19-23</sup> However, there is a paucity of data directly comparing any 2 of these approaches.<sup>18,24,25</sup>

### **Consensus Statement on Method of MRI Directed Biopsies**

While the use of advanced technology such as a fusion system or an in-bore biopsy system may be helpful, the superiority of any specific approach has not been established. One approach may be to apply different methods of MRI targeting depending on the characteristics of the lesion, for example, using an in-bore or fusion system for lesions that

are small or in a region difficult to access (ie the anterior or apical prostate), while limiting cognitive targeting to other lesions. While fusion and in-bore biopsy systems may have value in incrementally improving biopsy yield, they are expensive, and the existing literature supports cognitive targeting as a sound approach for facilitating the detection of CS cancer when advanced technologies are not available and when operators are skilled with image guided procedures.

#### **Consensus Statement on Additional Considerations for MRI Targeted Biopsy**

It is advised to obtain at least 2 cores from each MRI target, with a larger number of cores at the discretion of the operator based on lesion size and location as well as confidence in targeting accuracy. In addition, when performing MRI targeted biopsy, approaches to pain control as well as the prevention and management of bleeding and infectious complications are similar to those for systematic biopsy.<sup>26</sup> It is advised that systematic and MRI targeted cores be separately labeled for purposes of pathological analysis and reporting, given that current accepted clinical nomograms are derived from data based on standard systematic biopsy results.<sup>27</sup> In addition, the interpreting pathologist should routinely report the presence of inflammation, high grade prostatic intraepithelial neoplasia and atypical small acinar proliferation in targeted cores as the presence of a correlative histological abnormality may provide assurance that the MRI defined region of interest was accurately targeted when benign.<sup>25</sup>

#### **Consensus Statement on Need for Concurrent Systematic Sampling when Performing MRI Targeting**

The high sensitivity of MRI targeted cores for CS cancer raises the question of whether systematic cores are also warranted at the time of a MRI targeted repeat biopsy.<sup>28</sup> Numerous investigations indicate the presence of occasional CS cancers that are missed by targeted biopsy. While the frequency is variable, the data suggest some CS cancers detected by systematic biopsies are missed by targeted biopsy (0% to 23%), even with optimized conditions and expertise. The quality of MRI acquisition and interpretation as well as the targeting technique itself likely impact the detection of CS cancer. Nonetheless, some CS cancers falling below the threshold of MRI detection do exist. Thus, we advise that a case specific decision must be made regarding whether to perform concurrent systematic sampling at the targeted biopsy in order to maximize CS cancer detection. Deferral of concurrent systematic biopsy should only be considered when quality assurance has been performed to support the outcomes of MRI targeted biopsy in the local practice.

#### **Consensus Statement on Role of Immediate Re-biopsy after MRI**

The available data suggest that repeat biopsy in patients with persistent clinical suspicion for prostate cancer is justified in the setting of MRI with a PI-RADS 4 or 5 lesion (a highly suspicious lesion), and that deferral of repeat biopsy may be considered in the setting of a negative (PI-RADS 1) or low suspicion (PI-RADS 2) MRI in the absence of strong clinical suspicion. However, we believe that the data are insufficient to support routinely deferring repeat biopsy of lesions receiving a PI-RADS assessment category of 3, for which CS cancer rates after targeted biopsy have been highly variable. Additionally, the available data indicate that 5% to 15% of CS cancers remain undetected on MRI in the repeat biopsy setting.

Therefore, CS cancer can never be entirely excluded on the basis of negative MRI and continued clinical followup is warranted whenever repeat biopsy is deferred on the basis of normal or low suspicion MRI. While these considerations reflect the cumulative data of expert centers, application in individual practices warrants that practitioners assess the accuracy of MRI in their own hands to ensure the applicability of these summary statements.

### **Consensus Statement on Followup after Negative MRI Directed Biopsies**

Continued clinical followup and consideration of repeat biopsy remain warranted after a negative MRI targeted biopsy. Such followup can be performed through a combination of serial PSA measurements, digital rectal examination and possibly repeat MRI examinations. For a MRI lesion with very high suspicion (ie PI-RADS assessment category of 5) that is negative on targeted biopsy, an earlier repeat targeted biopsy should be considered.<sup>29</sup>

### **Consensus Statement on Role of Ancillary Markers in MRI Targeted Biopsies**

Nonimaging markers (ie PSA based measures as well as PCA3) are likely useful in further selecting patients with negative or low suspicion MRI (PI-RADS assessment category of 1 or 2, respectively) who may deserve a systematic biopsy despite MRI results. However, targeted biopsy remains warranted for intermediate or high suspicion MRI lesions despite results from these ancillary markers, given the consistently observed strong independent effect of the MRI suspicion score on cancer detection in multivariate models. Further investigation is warranted to identify which of these markers best complements MRI findings in the repeat biopsy setting.

## **SUMMARY**

After an initial negative biopsy there is an ongoing need for strategies to improve patient selection for repeat biopsy as well as the diagnostic yield from repeat biopsies. Many options exist for men with a previously negative biopsy. If a biopsy is recommended, prostate MRI and subsequent MRI targeted cores appear to facilitate the detection of CS disease over standardized repeat biopsy. Thus, when high quality prostate MRI is available, it should be strongly considered for any patient with a prior negative biopsy who has persistent clinical suspicion for prostate cancer and who is undergoing a repeat biopsy. The decision of whether to perform MRI in this setting must also take into account the results of any other biomarkers and the cost of the examination, as well as the availability of high quality prostate MRI interpretation. If MRI is done, it should be performed, interpreted and reported in accordance with PI-RADS v2 guidelines.<sup>30</sup> Experience of the reporting radiologist and biopsy operator is required to achieve optimal results.

Practices integrating prostate MRI into patient care are advised to implement quality assurance programs to monitor targeted biopsy results. Patients receiving a PI-RADS assessment category of 3 to 5 warrant repeat biopsy with image guided targeting. While TRUS-MRI fusion or in-bore MRI targeting may be valuable for more reliable targeting, especially for MRI lesions that are small or in difficult locations, in the absence of such targeting technologies cognitive (visual) targeting remains a reasonable approach in skilled hands. At least 2 targeted cores should be obtained from each MRI defined target. Given a

number of studies showing a proportion of missed CS cancers by MRI targeted cores, a case specific decision must be made whether to perform concurrent systematic sampling. However, performing solely targeted biopsy should only be considered once quality assurance efforts have validated the performance of prostate MRI interpretations and MRI targeted biopsies with results consistent with the published literature. In patients with negative or low suspicion MRI (PI-RADS assessment category of 1 or 2, respectively), other ancillary markers (ie PSA, PSAD, PSAV, PCA3, PHI, 4K) may be of value in identifying patients warranting repeat systematic biopsy, although further data are needed on this topic. If a repeat biopsy is deferred on the basis of MRI findings, then continued clinical and laboratory followup is advised and consideration should be given to incorporating repeat MRI in this diagnostic surveillance regimen.

### Abbreviations and Acronyms

<b>CDR</b>	cancer detection rate
<b>CS</b>	clinically significant
<b>MRI</b>	magnetic resonance imaging
<b>PI-RADS</b>	Prostate Imaging Reporting and Data System
<b>PSA</b>	prostate specific antigen
<b>TRUS</b>	transrectal ultrasound

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