Magnetic Resonance Imaging‒Targeted Biopsy of the Prostate

Policy Number: 7.01.152  Last Review: 10/2017
Origination: 3/2017  Next Review: 3/2018

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Magnetic Resonance Imaging‒Targeted Biopsy of the Prostate when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Magnetic resonance imaging‒targeted biopsy of the prostate may be considered medically necessary for diagnosis and active surveillance of prostate cancer.

When Policy Topic is not covered
N/A

Considerations
There is no specific CPT code for this procedure. It would likely be reported with a prostate biopsy code (55700-55706) and the MRI guidance code 77021.

Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Individuals:</strong></td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With suspicion of prostate cancer</td>
<td>• Magnetic resonance imaging‒targeted biopsy</td>
<td>• Standard transrectal ultrasound-guided biopsy</td>
<td>• Overall survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Disease-specific survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Test accuracy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Morbid events</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Quality of life</td>
</tr>
<tr>
<td><strong>Individuals:</strong></td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With prostate cancer and in</td>
<td>• Magnetic resonance imaging‒targeted biopsy</td>
<td>• Standard transrectal ultrasound-guided biopsy</td>
<td>• Overall survival</td>
</tr>
<tr>
<td>active surveillance</td>
<td></td>
<td></td>
<td>• Disease-specific survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Test accuracy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Morbid events</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Quality of life</td>
</tr>
</tbody>
</table>

Before a transrectal ultrasound-guided biopsy, a magnetic resonance imaging (MRI) scan can indicate where suspicious legions are in the prostate. MRI permits
a targeted biopsy (as opposed to a blind biopsy, which is the current standard of care). The use of an MRI-guided prostate biopsy serves 2 functions: (1) to identify areas in the prostate that could harbor a high-grade tumor; and (2) to divert attention from any clinically insignificant cancers that could be overtreated. In accomplishing the secondary function, patients are placed into 1 of 2 categories: those only needing to be managed by active surveillance; or those needing definitive intervention.

For individuals who have suspicion of prostate cancer who receive MRI-targeted biopsy, the evidence includes numerous prospective and retrospective studies of paired cohorts, 2 randomized controlled trials and systematic reviews and meta-analyses of these studies comparing MRI-targeted biopsy with transrectal ultrasound (TRUS)‒guided biopsy in detecting overall, clinically significant and clinically insignificant prostate cancers. Relevant outcomes are overall survival, disease-specific survival, test accuracy, morbid events, and quality of life. Studies on the use of MRI-targeted prostate biopsy have shown that the technology may diagnose more clinically significant cancers than TRUS biopsy and fewer clinically insignificant cancers, which might stratify patients for treatment and active surveillance. Considering the prognostic value of risk stratification based on prostate biopsy, better diagnostic accuracy is likely to identify patients more accurately with clinically significant prostate cancer leading to changes in management that would be expected to result in clinically meaningful outcomes in terms of survival or quality of life. The evidence is sufficient to determine that the technology results in a meaningful improvement in net health outcome.

For individuals who have prostate cancer and in active surveillance who receive MRI-targeted biopsy, the evidence includes a systematic review and observational studies of paired cohorts comparing MRI-targeted biopsy with TRUS biopsy in detecting pathologic progression of prostate cancer in terms of Gleason score and detection of higher grade (Gleason score ≥7) cancer. Relevant outcomes are overall survival, disease-specific survival, test accuracy, morbid events, and quality of life. Current evidence has suggested that, compared with TRUS biopsy, MRI-targeted biopsy is better at detecting those patients in active surveillance who have progressed and need definitive intervention. With the greater ability to detect prostate cancer with a Gleason score 7 or higher, which is a critical parameter for definitive therapy in prostate cancer, use of this biopsy guidance technique is likely to translate into positive clinically meaningful outcomes (eg, survival and quality of life) in this population. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Background**

**Prostate Cancer**

Prostate cancer is the most commonly diagnosed cancer and the third leading cause of cancer deaths among men in the United States, with an estimated 161,360 new cases and 26,730 deaths in 2017.¹ The diagnosis and grading of prostate cancer is performed by taking a biopsy of the prostate gland.
Diagnosis
A prostate biopsy typically is performed in men who have an elevated prostate-specific antigen (PSA) level or who present with symptoms. The purpose of the biopsy is to determine whether cancer is present and to determine tumor grade. Tumor grade (as measured by the Gleason score) is a major determinate in whether a patient is eligible for active surveillance (lower grade tumors) or a factor for determining definitive intervention (higher grade tumors). Patients on active surveillance undergo periodic follow-up prostate biopsies to assess cancer progression (upgrading of Gleason score).

Prostate biopsies are currently performed using transrectal ultrasound (TRUS) guidance with a 12-core sampling strategy. TRUS was introduced in the late 1980s; with this technique, tissue cores are obtained systematically under ultrasound guidance throughout the whole prostate, although this approach still represents blind biopsy of the prostate as to the location of the possible cancer. Before 12-core sampling, 6-core (sextant) sampling was thought to miss too many cases of cancer. However, the 12-core sampling method may overdiagnose clinically insignificant disease and underdiagnose clinically significant disease. Compared with subsequent prostatectomy, TRUS underestimates tumor grade up to 40% of the time and too often detects clinically insignificant disease.

Therefore, the ideal biopsy strategy would only identify men with prostate cancer of clinical significance to direct interventional therapy, and to minimize the detection of clinically insignificant prostate cancer and the risk of consequent overtreatment.

For men undergoing an initial biopsy for an elevated PSA, the systematic 12-core TRUS biopsy detection rate for prostate cancer is approximately 40% to 45%. If an initial 12-core biopsy is negative, and there is still a clinical suspicion of cancer, subsequent serial 12-core biopsies may detect cancer, or, other biopsy techniques such as transperineal template-guided saturation biopsy (in which 30-80 cores are typically obtained) may be used. Saturation biopsy allows for anterior and apical sampling and may detect significant cancer, but also oversamples insignificant types of cancer. In addition, transperineal biopsy requires general anesthesia and is associated with increased morbidity.

Multiparametric magnetic resonance imaging (MRI) includes anatomic T2-weighted imaging for localization of the normal gland and cancer foci and 2 functional imaging techniques: diffusion-weighted and perfusion imaging. Multiparametric MRI evaluation permits identifying tumor location and extent, oversampling areas of interest, undersampling (or not sampling nontarget areas), and sampling of clinically significant disease (higher grade tumor). T2-weighted images reflect water content of tissues and can define the zonal anatomy of the prostate and the presence of prostate cancer as focal areas of low-signal intensities. The degree of intensity decrease differs with Gleason score; higher Gleason score prostate cancer shows lower signal intensities. False-positive findings can occur with benign abnormalities including prostatitis, atrophy, fibrosis, gland hyperplasia, or irradiation or hormonal treatment effects. Diffusion-weighted images measure the
random motion of water molecules. Low diffusion coefficients are associated with prostate cancer, and there is an inverse correlation between these values and Gleason score; however, confidence intervals overlap. Perfusion imaging permits assessment of contrast kinetics in focal lesions; prostate cancer typically enhances faster and to a greater extent than the surrounding prostate; however, the nonspecificity of patterns limits the usefulness of this technique in isolation.

Several methods of MRI guidance are available for prostate biopsy: cognitive (or visual), direct (“in-bore”), and MRI-ultrasound fusion (visual targeted or software-based targeted). Image fusion is the process of combining information from more than 1 image into a single image, which may be more informative than any of the images separately. Based on MRI, suspicious areas are identified (ie, regions of interest) and subjected to targeted biopsy.

With the visual method, the ultrasound operator simply aims the biopsy needle at the area of the prostate where prior MRI indicated the lesion. This method requires the MRI unit, a conventional TRUS facility, and an ultrasound operator with no additional training beyond TRUS biopsy. The disadvantage is the potential for human error in the extrapolation from MRI to TRUS without an overlay of the images.

Direct (in-bore) MRI-targeted biopsy requires the MRI tube, fusion of a prior MRI demonstrating a lesion with a contemporaneous MRI to confirm biopsy needle location, and needles introduced into the regions of interest. Serial MRI scans are performed to confirm biopsy needle placement. Studies have demonstrated that in-bore MRI-targeted biopsies have a median cancer detection rate significantly higher than random biopsies; however, this technique is time-consuming and costly, including the in-bore time and the 2 MRI sessions necessary. In addition, only suspicious lesions are sampled, because tissues with a “normal” appearance on MRI are not obtained.

MRI-TRUS fusion biopsy, done visually or using software, superimposes preprocedure (stored) MRI over an intraprocedure (real-time) ultrasound to direct the biopsy needle to an ultrasound region of interest defined by multiparametric MRI.

Currently, there is evidence comparing these three techniques in terms of their ability to detect overall or clinically significant prostate cancer; available results are summarized in the Technical Performance subsection of the Rationale.

Proposed clinical indications for use of MRI-targeted prostate biopsy include: (1) as initial biopsy, (2) rebiopsy after a first negative standard biopsy in men with persistent suspicion of disease, including those with persistently increased PSA levels, suspicious digital rectal exam, previous biopsy with an atypical focus on histology, or extensive high-grade prostatic intraepithelial neoplasia, (3) follow-up for active surveillance to determine initial eligibility for active surveillance and assessing progression disease over time, and (4) for local recurrence after radical
prostatectomy, after external-beam radiotherapy, or after high-intensity focused ultrasound.

**Regulatory Status**
MRI-targeted or MRI-TRUS fusion biopsy is a medical procedure that uses MRI and ultrasound devices previously approved by the U.S. Food and Drug Administration (FDA). Prostate biopsy is a surgical procedure and, as such, is not subject to regulation by the FDA.

FDA product code, ultrasound devices: IYN, ITX, IYO. FDA product code, MRI devices: LNH, LNI, MOS.

Several MRI-US fusion software-based targeted prostate biopsy platform specifications have been cleared for marketing by FDA through the 510(k) process. Fusion software include Artemis™ (Eigen, Grass Valley, CA), BioJet™ (D&K Technologies, Gurajat, India), BiopSee® (MedCom, Columbia, SC), Real-time Visual Sonography (Hitachi, Tokyo, Japan), UroNav™ (Invivo/Philips, Gainesville, FL), Urostation® (Koelis, Auburndale, MA), and Virtual Navigator (Esaote, Genoa, Italy).

**Rationale**
This evidence review was created in October 2015 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through July 12, 2017.

The literature consists of numerous prospective and retrospective studies of paired cohorts as well as systematic reviews and meta-analyses of these studies. Appendix Table 1 lists all studies included in systematic review and meta-analyses assessed herein.

Assessment of a diagnostic technology typically focuses on 3 categories of evidence: (1) its technical performance (test-retest reliability or interrater reliability); (2) diagnostic accuracy (sensitivity, specificity, and positive and negative predictive value) in relevant populations of patients; and (3) clinical utility (ie, demonstration that the diagnostic information can be used to improve patient outcomes).

**Magnetic Resonance Imaging–Targeted Biopsy vs Standard Biopsy for Detection of Prostate Cancer**

**Clinical Context and Test Purpose**
The purpose of magnetic resonance imaging (MRI)–targeted prostate biopsy in men who have an elevated prostate-specific antigen (PSA) level or who present with symptoms is to inform a decision whether the patient has prostate cancer that requires definitive treatment or active surveillance for prostate cancer.
The question addressed in this evidence review is: Do MRI-targeted prostate biopsy techniques result in an improved health outcome compared with 12-core transrectal ultrasound (TRUS)-guided biopsy among biopsy-naive or previously biopsy-negative patients?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant populations of interest are biopsy-naive or previously biopsy-negative men with elevated PSA levels and/or clinical symptoms of prostate cancer.

**Interventions**
The relevant interventions of interest are MRI-targeted prostate biopsy techniques: cognitive (or visual), MRI-in-bore, and MRI-TRUS fusion (visual targeted or software-based targeted)

**Comparators**
The following test is currently being used to make decisions about the diagnosis of prostate cancer: 12-core TRUS-guided prostate biopsy.

**Outcomes**
The general outcomes of interest are diagnostic accuracy (ie, test accuracy and validity) of clinically significant prostate cancer and health outcomes (ie, survival, quality of life).

Specific outcomes are improving the detection of clinically significant prostate cancer and increasing accurate risk stratification are the outcomes of primary interest because they would inform patient’s treatment plan and consequently, impact health outcomes.

False-positive test results can lead to overdiagnosis and overtreatment, which exposes patients to potential treatment morbidity without benefit.

False-negative test results can lead to failure to diagnose clinically significant cancers that require definitive treatment.

**Timing**
The timeframe for determining diagnostic accuracy is several weeks based on any confirmatory testing needed. Among patients with no sign that the cancer has spread outside of the prostate, the relative 5-year survival rate is nearly 100%, and, including all stages of prostate cancer the relative 5-year survival rate is 99% and the 15-year survival rate is 96%. Therefore, the timeframe for evaluation of survival in prostate cancer is approximately 10 to 20 years.

**Setting**
Prostate biopsy is generally done on an outpatient basis.
Technical Performance
Currently, there are no studies assessing the interrater reliability of MRI-targeted prostate biopsy.

Comparisons of Different MRI-Targeted Biopsy Techniques
Wegelin et al (2017) conducted a systematic review of observational studies and compared pooled sensitivity rates for outcomes for detecting overall and clinically significant prostatic cancer using 3 MRI-targeted biopsy techniques (cognitive MRI, MRI-in-bore, MRI-TRUS) among biopsy-naive or previously negative patients. The studies used both MRI-targeted and TRUS-guided biopsy techniques on the study subjects. For detection of overall prostate cancer, 7 studies used cognitive MRI-targeted biopsy to perform targeting (n=712 patients) with a pooled sensitivity of 72% (95% confidence interval [CI], 62% to 81%), 14 studies used MRI-TRUS fusion biopsy (n=2817 patients) with a pooled sensitivity of 81% (95% CI, 75% to 85%), and 3 studies used MRI-in-bore targeted biopsy (n=305 patients) with a pooled sensitivity of 89% (95% CI, 78% to 95%). MRI-in-bore targeted biopsy had a statistically significant higher sensitivity rate in detecting overall prostatic cancer (p=0.02) than cognitive MRI-targeted biopsy. There were no significant differences in the performance of MRI-TRUS fusion biopsy compared with MRI-in-bore (p=0.13), or for MRI-TRUS fusion biopsy compared with cognitive MRI-targeted biopsy (p=0.11).

For clinically significant prostate cancer, 3 studies used cognitive MRI-targeted biopsy to perform targeting (n=220 patients) with a pooled sensitivity of 86% (95% CI, 69% to 94%), 8 studies used MRI-TRUS fusion biopsy (n=2114 patients) with a pooled sensitivity of 89% (95% CI, 82% to 93%), and 2 studies used direct (in-bore) MRI-targeted biopsy (n=163 patients) with a pooled sensitivity of 92% (95% CI, 76% to 98%). There was no significant advantage of the usage of any one technique of MRI-targeted biopsy for the detection of clinically significant prostate cancer (MRI-in-bore vs MRI-TRUS fusion biopsy, p=0.60; MRI-in-bore vs cognitive MRI-targeted biopsy, p=0.42; MRI-TRUS fusion biopsy vs cognitive MRI-targeted biopsy, p=0.62).

Schoots et al (2015) conducted a systematic review, selecting 14 studies comparing outcomes of one navigational system with another, of which only eight presented data on the detection of significant and insignificant prostate cancer. Two studies used cognitive MRI-targeted, five used MRI-TRUS fusion, and one used MRI-in-bore targeted biopsy. MRI-TRUS fusion and MRI-in-bore targeted biopsy significantly improved prostate cancer detection rates compared with TRUS biopsy (relative sensitivity, 1.29 [95% CI, 1.16 to 1.43] vs relative sensitivity, 1.26 [95% CI, 1.08 to 1.46], respectively). Cognitive MRI-targeted biopsy did not show much improvement compared with TRUS biopsy (relative sensitivity, 1.03; 95% CI, 0.91 to 1.16).

Arsov et al (2015) conducted a prospective randomized trial in Germany comparing MRI-in-bore (arm A) with MRI-TRUS fusion biopsy and additional systematic 12-core TRUS-guided prostate biopsy (arm B) in patients with prior negative biopsies. In interim analysis, arm B did not significantly improve the
overall prostate cancer detection rate (the primary end point), and the trial was halted. The trial enrolled 267 patients, of whom 210 were analyzed (106 randomized to arm A, 104 to arm B). The prostate cancer detection rate was 37% in arm A and 39% in arm B (95% CI for difference, -16% to 11%; p=0.7). Detection rates for clinically significant prostate cancer (29% vs 32%; p=0.7) and the highest percentage tumor involvement per biopsy core (48% vs 42%; p=0.4) were similar between arms.

Section Summary: Technical Performance
Existing evidence from 2 systematic reviews and a randomized controlled trial (RCT) has suggested performance similar to MRI-TRUS fusion and in-bore MRI-targeted biopsy in detecting clinically significant prostate cancer. There is inconsistent evidence whether cognitive MRI-targeted biopsy performs as well as MRI-TRUS fusion or in-bore MRI-targeted biopsy.

Diagnostic Accuracy

Systematic Reviews
Wu et al (2015) published a systematic review and meta-analysis (literature search through May 2015) to determine whether MRI-TRUS fusion biopsy is better than standard systematic biopsy in detecting prostate cancer. In 16 trials (1 RCT, 15 paired cohort studies), a total of 3105 participants underwent MRI-TRUS fusion or TRUS-guided biopsy (see Table 1). Reviewers evaluated the quality of each trial using the Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS-2). While there was variation in the methodologic quality of selected studies, none were judged to be at an overall risk of bias. MRI-TRUS fusion biopsy had a higher detection rate of overall prostate cancer diagnosis than TRUS-guided biopsy, with moderate heterogeneity between trials (see Tables 2, 3). Among 10 trials that compared the detection rate of clinically significant prostate cancer between these 2 techniques, MRI-TRUS fusion biopsy had a higher detection rate (36% [892/2481] men with MRI-TRUS fusion biopsy) compared with that of TRUS-guided biopsy (30% [786/2583] men with TRUS-guided biopsy), with no heterogeneity between trials. MRI-TRUS fusion biopsy [255 (11%) of 2395 men with MRI-TRUS fusion biopsy] had a lower detection rate of clinically insignificant prostate cancer compared with TRUS-guided systematic biopsy (15% [368/2494] men with TRUS-guided biopsy).

A 2015 systematic review and meta-analysis by Schoots et al (literature search through May 2014) assessed the diagnostic differences between MRI-targeted biopsy and TRUS-guided biopsy in detecting overall prostate cancer (the primary objective) and clinically significant and insignificant prostate cancer (the secondary objective) (see Table 1). Selected studies included men with suspected prostate cancer scheduled for transrectal biopsy because of increased prostate-specific antigen levels and/or positive digital rectal exam. Overall, based on QUADAS criteria, the methodologic quality of the studies was deemed to be fair. Only studies that included MRI-targeted and TRUS-guided biopsy in each patient were selected. Therefore, all men had a positive MRI, defined as a suspicious lesion on prostate MRI scan. Reports on transperineal or saturation biopsy were excluded.
The sensitivity of each technique was calculated as the number of positive diagnostic results by the technique divided by the total number of cancers detected by both the techniques combined (the total number of cancers was calculated as the number of concordant positive results plus the number of discordant results for which either test was positive). Relative sensitivity was the sensitivity ratio between MRI-targeted and TRUS-guided biopsy. A relative sensitivity of greater than one indicated that MRI-targeted biopsy detected more cancers than TRUS-guided biopsy, and a relative sensitivity less than one indicated that MRI-targeted biopsy detected fewer cancers than TRUS-guided biopsy. Analyses were performed for two predefined subgroup categories: (1) men undergoing initial biopsy, men with a previous negative biopsy, and men with mixed results for initial vs subsequent biopsy; and (2) men who received direct vs fusion biopsy MRI. Sixteen studies with 1926 men were eligible. MRI-targeted and TRUS-guided biopsy did not differ significantly in their overall prostate cancer detection rates (sensitivity, 85% [95% CI, 80% to 89%] vs sensitivity, 81% [95% CI, 70% to 88%], respectively; see Table 2, 3). Ten studies presented data on the rates of detection of significant vs insignificant prostate cancer. Of the 10 studies, 5 reported results for initial biopsy, 2 for a previous negative biopsy, and 3 with a mixed population. MRI-targeted biopsy had a higher rate of detection of significant prostate cancer than TRUS-guided biopsy (sensitivity, 91% [95% CI, 87% to 94%] vs sensitivity, 76% [95% CI, 64% to 84%]) and a lower rate of detection of insignificant prostate cancer (sensitivity, 44% [95% CI, 26% to 64%] vs sensitivity, 83% [95% CI, 77% to 87%]), respectively. The relative improvement in significant prostate cancer detection by MRI-targeted biopsy was in men with previous negative biopsy, but not in men undergoing initial biopsy (relative sensitivity, 1.54 [95% CI, 1.05 to 2.57] vs relative sensitivity, 1.10 [95% CI, 1.00 to 1.22]).

Wegelin et al (2017) conducted a systematic review and meta-analysis (literature search through October 2014) to evaluate whether MRI-targeted biopsy techniques had higher detection rates of clinically significant prostate cancer than TRUS-guided biopsy. Twenty-five studies compared detection rates of overall prostate cancer, while 14 studies compared detection rates of both clinically significant and clinically insignificant between MRI-targeted and TRUS-guided biopsy techniques. There was no significant difference between MRI-targeted (all techniques combined) (sensitivity, 81%; 95% CI, 76% to 85%) and TRUS-guided biopsy (sensitivity, 83%; 95% CI, 77% to 88%) for overall prostate cancer detection. MRI-targeted biopsy (sensitivity, 90%; 95% CI, 85% to 94%) had higher sensitivity to detect clinically significant prostate cancer than TRUS-guided biopsy (sensitivity, 79%; 95% CI, 68% to 87%). MRI-targeted biopsy (sensitivity, 7%; 95% CI, 4% to 10%) had lower sensitivity to detect clinically insignificant prostate cancer than TRUS-guided biopsy (sensitivity, 14%; 95% CI, 11% to 18%).

Subsection Summary: Systematic Reviews
Systematic reviews and meta-analyses of observational studies have consistently reported superior sensitivity of the MRI-targeted biopsy techniques in detecting clinically significant prostate cancer compared with TRUS-guided biopsy.
### Table 1. Characteristics of the Systematic Reviews Comparing Prostate Cancer Detection Rates Between MRI-Targeted Biopsy and Systematic/TRUS-Guided Biopsies

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Dates</th>
<th>Trials</th>
<th>N (Range)</th>
<th>Design</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu et al (2015)</td>
<td>To May 2015</td>
<td>16</td>
<td>3105 (30-1003)</td>
<td>1 RCT, 15 cohort studies</td>
<td>Overall detection rate, clinically significant and clinically insignificant prostate cancer detection rate (MRI-TRUS fusion vs standard TRUS biopsy)</td>
</tr>
<tr>
<td>Schoots et al (2015)</td>
<td>To May 2014</td>
<td>16</td>
<td>1926 (32-582)</td>
<td>Paired cohort (sequential sampling for 2 biopsy techniques in same individual)</td>
<td>Overall detection rate, clinically significant and clinically insignificant prostate cancer detection rate (MRI-targeted vs standard TRUS biopsy)</td>
</tr>
<tr>
<td>Wegelin et al (2017)</td>
<td>Oct 2014</td>
<td>25</td>
<td>3520 (20-1003)</td>
<td>Paired cohort (sequential sampling for 2 biopsy techniques in same individual)</td>
<td>Overall detection rate, clinically significant and clinically insignificant prostate cancer detection rate (MRI-targeted vs standard TRUS biopsy)</td>
</tr>
</tbody>
</table>

MRI: magnetic resonance imaging; RCT: randomized controlled trial; TRUS: transrectal ultrasound.

### Table 2. Outcomes From Systematic Reviews Comparing Relative Risk and Relative Sensitivity for Prostate Cancer Detection Between MRI-Targeted Biopsy and Systematic/TRUS-Guided Biopsies

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Trials</th>
<th>n/N</th>
<th>Outcomes</th>
<th>RR/Relative Sensitivity</th>
<th>95% CI</th>
<th>p</th>
<th>I², %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu et al (2015)</td>
<td>16</td>
<td>3013/3105</td>
<td>Detection rate of prostate cancer</td>
<td>1.06</td>
<td>1.01 to 1.12</td>
<td>0.03</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>2481/2583</td>
<td>Detection rate of clinically significant prostate cancer</td>
<td>1.19</td>
<td>1.10 to 1.29</td>
<td>&lt;0.01</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>2395/2494</td>
<td>Detection rate of clinically insignificant prostate cancer</td>
<td>0.68</td>
<td>0.59 to 0.79</td>
<td>&lt;0.01</td>
<td>72</td>
</tr>
<tr>
<td>Schoots et al (2015)</td>
<td>16</td>
<td>1926</td>
<td>Detection rate of prostate cancer</td>
<td>1.05</td>
<td>0.94 to 1.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>1657</td>
<td>Detection rate of clinically significant prostate cancer</td>
<td>1.20</td>
<td>1.09 to 1.32</td>
<td></td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>1657</td>
<td>Detection rate of clinically insignificant prostate cancer</td>
<td>0.56</td>
<td>0.37 to 0.85</td>
<td></td>
<td>78</td>
</tr>
<tr>
<td>Wegelin et al (2017)</td>
<td>25</td>
<td>3520</td>
<td>Detection rate of prostate cancer</td>
<td>0.98</td>
<td>0.90 to 1.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>2328</td>
<td>Detection rate of clinically significant</td>
<td>1.16</td>
<td>1.02 to 1.32</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Outcomes From Systematic Reviews Comparing Prostate Cancer Detection Rates Between MRI-Targeted Biopsy and Systematic/TRUS-Guided Biopsies

<table>
<thead>
<tr>
<th>Study</th>
<th>Cancer Detection Rate/ Sensitivity, n/N or % (95% CI)</th>
<th>Trials</th>
<th>Measure</th>
<th>Association</th>
<th>95% CI</th>
<th>p</th>
<th>$I^2$, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu et al (2015)</td>
<td>14/2328</td>
<td>14</td>
<td>Relative risk</td>
<td>0.47</td>
<td>0.35 to 0.63</td>
<td>0.03</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>2328/3105</td>
<td>14</td>
<td>Relative risk</td>
<td>1.06</td>
<td>1.01 to 1.12</td>
<td>&lt;0.01</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3105/3103</td>
<td>14</td>
<td>Relative risk</td>
<td>1.19</td>
<td>1.10 to 1.29</td>
<td>&lt;0.01</td>
<td>0</td>
</tr>
<tr>
<td>Schoots et al (2015)</td>
<td>14/2328</td>
<td>4</td>
<td>Relative sensitivity</td>
<td>0.68</td>
<td>0.59 to 0.79</td>
<td>&lt;0.01</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>2328/3105</td>
<td>4</td>
<td>Relative sensitivity</td>
<td>1.05</td>
<td>0.94 to 1.19</td>
<td>0.03</td>
<td>88</td>
</tr>
<tr>
<td>Wegelin et al (2017)</td>
<td>14/2328</td>
<td>3</td>
<td>Relative sensitivity</td>
<td>0.47</td>
<td>0.35 to 0.63</td>
<td>0.07</td>
<td>28</td>
</tr>
</tbody>
</table>

CI: confidence interval; MRI: magnetic resonance imaging; RR: relative risk; TRUS: transrectal ultrasound.

Randomized Controlled Trials
Porpiglia et al (2017) published a single-center RCT in Italy among 212 biopsy-naive patients with suspected prostate cancer (prostate-specific antigen level ≤15 ng/mL and negative digital rectal examination results). Patients were randomized to a prebiopsy multiparametric MRI (mpMRI) group (n=107) or a standard biopsy group (n=105) (see Table 4). The mpMRI was performed with a 1.5-Tesla scanner using a 32-channel phase array coil or 4-channel phase array coil combined with an endorectal coil. Patients in mpMRI group underwent MRI-TRUS fusion biopsy if they had mpMRI evidence of suspected prostate cancer lesions (n=81); others in this group underwent standard biopsy (n=26). The uropathologist who conducted...
the histopathologic examination was blinded to the inclusion of each patient in the RCT and the mpMRI results. In the intention-to-treat analysis, the detection rate was higher in mpMRI group than in the standard biopsy group for overall prostate cancer and for clinically significant prostate cancer (see Table 5). In the as-treated analysis, the MRI-TRUS fusion biopsy approach had a significantly higher detection rate (vs those undergoing standard biopsy from mpMRI group or the standard biopsy group) of overall prostate cancer (61% vs 19% vs 30%, respectively; p<0.001) and for clinically significant prostate cancer (57% vs 4% vs 18%, respectively; p<0.001).

In 2016, Baco et al reported on a single-center RCT in Norway that included 175 biopsy-naive patients with suspicion for prostate cancer (PSA increased to 4-20 ng/mL: and/or abnormal digital rectal exam results) randomized to an MRI-TRUS fusion biopsy group (n=86) or a control group (2 targeted biopsy from palpable lesions followed by 12-core systematic random biopsy; n=89) to compare detection rates for overall and clinically significant prostate cancers (see Table 4). Prebiopsy MRI was performed in all patients randomized to the MRI group using a 1.5-T Avanto scanner without an endorectal coil. Uropathologists performing the histopathologic analyses were not blinded to study group assignments. Detection rates for overall prostate cancer and clinically significant prostate cancer did not significantly differ between MRI-TRUS fusion biopsy and control groups (see Table 5). While comparing detection of clinically significant cancer by MRI-targeted biopsy (n=66) with random biopsy only in the control group (n=60) among patients with normal digital rectal exam results, there was no significant difference in detection rates (21% vs 25%, respectively, p=0.7).

**Subsection Summary: Randomized Controlled Trials**

While the Porpiglia RCT demonstrated the superiority of MRI-targeted biopsy in detecting overall and clinically significant prostate cancer, the Baco RCT did not find a significant difference between these techniques. Studies have suggested that MRI using endorectal coils provided superior spatial resolution and superior sensitivity to detect prostate cancer compared with MRI not using endorectal coils, which might explain the failure of the Baco trial to demonstrate the superiority of MRI-targeted biopsy in detecting clinically significant cancer compared with TRUS biopsy among patients with suspicion for prostate cancer with normal digital rectal exam results.

**Table 4. Randomized Controlled Trial Outcomes Comparing Prostate Cancer Detection Rates Between MRI-Targeted Biopsy and Systematic/TRUS-Guided Biopsies**

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Countries</th>
<th>Site(s)</th>
<th>Population</th>
<th>Dates</th>
<th>MRI-TRUS Fusion Biopsy</th>
<th>Standard Biopsy</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porpiglia et al (2016)</td>
<td>Italy</td>
<td>1</td>
<td>Biopsy-naive men with PSA ≤15 ng/mL and</td>
<td>2014-2016</td>
<td>107 (81 targeted biopsy, 26 standard biopsy)</td>
<td>105</td>
<td>Overall and clinically significant prostate cancer</td>
</tr>
</tbody>
</table>
negative DRE detection rates

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baco et al (2016)</td>
<td>Biopsy-naive men with PSA 4-20 ng/mL and/or abnormal DRE</td>
<td>2011-2013 86 89 Overall and clinically significant prostate cancer detection rates</td>
</tr>
</tbody>
</table>

DRE: digital rectal exam; MRI: magnetic resonance imaging; PSA: prostate-specific antigen; TRUS: transrectal ultrasound.

### Table 5. Summary of Findings From Randomized Controlled Trials Comparing Prostate Cancer Detection Rates Between MRI-Targeted Biopsy and Systematic/TRUS-Guided Biopsies

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porpiglia et al (2016)</td>
<td>Overall prostate cancer detection</td>
<td>43.9 (47/107) vs 18.1 (19/107) &lt;0.001</td>
</tr>
<tr>
<td>Baco et al (2016)</td>
<td>Clinically significant prostate cancer detection</td>
<td>50.5 (54/107) vs 29.5 (31/105) 0.002</td>
</tr>
<tr>
<td></td>
<td>Overall prostate cancer detection</td>
<td>59 (51/86) vs 54 (48/89) 0.4</td>
</tr>
<tr>
<td></td>
<td>Clinically significant prostate cancer detection</td>
<td>44% (38/86) vs 49% (44/89) 0.5</td>
</tr>
</tbody>
</table>

MRI: magnetic resonance imaging; TRUS: transrectal ultrasound.

### Observational Studies

Siddiqui et al (2015) reported on a single-center prospective cohort study of 1003 men with elevated PSA levels or abnormal DRE results undergoing both MRI-TRUS fusion biopsy and standard biopsy concurrently from 2007 through 2014 (see Table 6). There was no statistically significant difference in overall prostate cancer detection, however, MRI-TRUS fusion biopsy diagnosed 30% more high-risk cancers (Gleason score ≥4+3) than standard biopsy (173 cases vs 122 cases, p<0.001) and 17% fewer low-risk (Gleason score 3+3 or low volume 3+4) types of cancer (213 cases vs 258 cases, p<0.001) (see Table 7), respectively. Among 170 patients who underwent prostatectomy with whole-gland pathology, the predictive ability of the MRI-TRUS fusion biopsy in differentiating low-risk from intermediate- (Gleason score high volume 3+4) and high-risk disease was greater than that of standard biopsy or both approaches combined (see Table 8). The sensitivity rates to detect intermediate- to high-risk prostate cancer using MRI-targeted, standard, and combined biopsy were 77% (95% CI, 67% to 84%), 53% (95% CI, 43% to 63%), and 85% (76% to 91%), respectively. Accuracy rates to detect intermediate- to high-risk prostate cancer using MRI-targeted, standard and combined biopsy were 73% (95% CI, 70% to 76%), 59% (95% CI, 55% to 63%), and 69% (65% to 72%), respectively. The authors conducted a decision-curve analysis among this population (n=170) to compute the net benefit of decisions for prostatectomy based on biopsy results from MRI-targeted biopsy alone, systematic biopsy alone, and combined biopsy. The benefit was defined as
surgical intervention limited to intermediate- and high-risk tumors, while harm was the surgical procedure for low-risk tumors. The area under the curve (or net benefit) was highest for MRI-targeted biopsy (0.73). The area under the curve for systematic biopsy and combined biopsy was 0.59 and 0.67, respectively (p<0.05 for all comparisons; see Table 8).

In 2016, Filson et al reported a single-center prospective study among 1042 men with either (1) an elevated PSA level or abnormal digital rectal examination result, or (2) confirmation of low-risk prostate cancer for patients considering active surveillance. All patients underwent an mpMRI and regions of interest (ROIs) were graded as 1 to 5. Men with ROIs underwent targeted MRI-TRUS fusion biopsy followed by TRUS-guided biopsy for detection of clinically significant prostate cancer (Gleason score ≥7). A total of 825 (79%) patients had at least 1 ROI of grade 3 or more, and 217 (21%) had no suspicious lesions noted on MRI (see Table 6). Among 825 patients with one or more ROI of grade 3 or higher, combination of MRI-TRUS fusion and TRUS-guided biopsy (combined biopsy) identified 289 cases of clinically significant prostate cancer (vs 229 cases for MRI-TRUS fusion only and 199 cases for systematic biopsy only; p<0.001). A total of 204 men were diagnosed with a Gleason score 6 disease using combined biopsy (vs 208 with systematic only [p<0.001] and 131 with MRI-TRUS fusion only [p<0.001]; see Table 7).

### Table 6. Characteristics of Observational Studies Comparing Prostate Cancer Detection Rates Among Participants Undergoing Both MRI-Targeted and Systematic/TRUS-Guided Biopsies

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Type</th>
<th>Location</th>
<th>Dates</th>
<th>MRI-TRUS Fusion Biopsy</th>
<th>Standard Biopsy</th>
</tr>
</thead>
</table>

MRI: magnetic resonance imaging; TRUS: transrectal ultrasound.

### Table 7. Summary of Findings From Nonrandomized/Observational Studies Comparing Prostate Cancer Detection Rates Among Participants Undergoing Both MRI-Targeted and Systematic/TRUS-Guided Biopsies

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>High-Risk/Clinically Significant Prostate Cancer</th>
<th>Detection Rate, % (n/N)</th>
<th>p</th>
<th>Overall Prostate Cancer</th>
<th>Detection Rate, % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siddiqui et al (2015)</td>
<td>MRI-TRUS fusion</td>
<td>17 (173/1003) (^a)</td>
<td>&lt;0.01 (^c)</td>
<td>MRI-TRUS fusion</td>
<td>46 (461/1003)</td>
</tr>
<tr>
<td></td>
<td>TRUS-guided systematic</td>
<td>12 (122/1003) (^a)</td>
<td>&lt;0.01 (^c)</td>
<td>TRUS-guided systematic</td>
<td>47 (469/1003)</td>
</tr>
<tr>
<td>Filson et al (2016)</td>
<td>MRI-TRUS fusion only</td>
<td>28 (229/825) (^b)</td>
<td>&lt;0.01 (^c)</td>
<td>Targeted MRI-TRUS fusion</td>
<td>44 (360/825)</td>
</tr>
<tr>
<td></td>
<td>Artemis-guided systematic only</td>
<td>24 (199/825) (^b)</td>
<td>&lt;0.01 (^c)</td>
<td>Systematic</td>
<td>49 (307/825)</td>
</tr>
</tbody>
</table>
MRI: magnetic resonance imaging; RR: relative risk; TRUS: transrectal ultrasound.

<table>
<thead>
<tr>
<th>High-risk (Gleason score ≥4+3) cancer detection rate.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically significant (Gleason score ≥7, both ≥4+3 or ≥3+4) cancer detection rate.</td>
</tr>
<tr>
<td>McNemar test p value.</td>
</tr>
</tbody>
</table>

Table 8. Performance of Different Biopsy Approaches in Detecting Intermediate- to High-Risk Prostate Cancer on Whole-Gland Prostatectomy Specimen in Siddiqui et al

<table>
<thead>
<tr>
<th>Variables</th>
<th>Targeted MRI-TRUS Fusion Biopsy</th>
<th>Standard Extended-Sextant Biopsy</th>
<th>Combined Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (95% CI), %</td>
<td>77 (67 to 84)</td>
<td>53 (43 to 63)</td>
<td>85 (76 to 91)</td>
</tr>
<tr>
<td>Specificity (95% CI), %</td>
<td>68 (57 to 78)</td>
<td>66 (54 to 76)</td>
<td>49 (37 to 60)</td>
</tr>
<tr>
<td>Negative predictive value (95% CI), %</td>
<td>70 (58 to 80)</td>
<td>53 (43 to 63)</td>
<td>73 (58 to 84)</td>
</tr>
<tr>
<td>Positive predictive value (95% CI), %</td>
<td>75 (65 to 83)</td>
<td>66 (54 to 76)</td>
<td>67 (58 to 75)</td>
</tr>
<tr>
<td>Accuracy (95% CI), %</td>
<td>73 (70 to 76)</td>
<td>59 (55 to 63)</td>
<td>69 (65 to 72)</td>
</tr>
<tr>
<td>AUC (95% CI), %</td>
<td>0.73 (0.66 to 0.79)</td>
<td>0.59 (0.52 to 0.67)</td>
<td>0.67 (0.60 to 0.74)</td>
</tr>
<tr>
<td>P value of comparison with targeted MRI-TRUS fusion biopsy</td>
<td>0.005</td>
<td>0.04</td>
<td></td>
</tr>
</tbody>
</table>

AUC: area under the curve; CI: confidence interval; MRI: magnetic resonance imaging.

**Subsection Summary: Observational Studies**

There is consistent evidence that MRI-TRUS fusion biopsies have superior sensitivity compared with TRUS-guided biopsy in detecting clinically significant prostate cancer. Comparison of this diagnostic test’s ability to detect overall and clinically significant cancers with prostatectomy finding as the reference by Siddiqui et al further strengthen the evidence supporting the superiority of MRI-TRUS fusion over TRUS-guided biopsy in the diagnosis of prostate cancer.

**Section Summary: Diagnostic Accuracy**

Multiple systematic reviews and meta-analyses of paired cohort studies have consistently reported the superiority of MRI-targeted biopsy over the systematic/TRUS-guided biopsies in the diagnosis of prostate cancer among biopsy-naive or previously negative prostate cancer patients. Among the 2 recent RCTs, Porpiglia et al (2017) reported MRI-targeted biopsy to have a better detection rate for clinically significant prostate cancer. In the other RCT, Baco et al did not use an endorectal coil in prebiopsy MRI, which might have resulted in an inferior sensitivity of MRI in detecting prostate cancer and might explain the lack of statistically significant difference between targeted MRI and TRUS biopsy in their trial. Siddiqui et al (2015) reported a superior test validity and higher net benefit of using MRI-targeted compared with systematic biopsy with whole-gland prostatectomy specimen as a reference standard further strengthens the evidence supporting the superiority of MRI-targeted biopsies over TRUS-guided biopsies in the detection of clinically significant prostate cancer.
Clinical Utility
Currently, there is no direct evidence from studies demonstrating that MRI-targeted prostate biopsies result in improved patient outcomes (eg, survival or quality of life). However, there is strong evidence in favor of the prognostic value of the Gleason score based on prostate biopsy. Pierorazio et al (2013) conducted a retrospective study using the Johns Hopkins Radical Prostatectomy Database to examine the correlation between Gleason score and pathologic stage and biochemical recurrence in 6462 men. Almost 95% of patients with cancer with a Gleason score of 6 on needle biopsy did not show signs of biochemical recurrence at 5 years after radical prostatectomy. The study also reported that a tumor with Gleason score 3+4=7 tumor on biopsy had an estimated 5-year biochemical recurrence-free survival of 83%.

Antonarakis et al (2012) conducted a retrospective analysis of 450 men who underwent prostatectomy and subsequently developed PSA recurrence (≥0.2 ng/mL) to describe the metastasis-free survival and define clinical prognostic factors modifying metastasis risk. Among the 450 patients with a mean follow-up of 8 years, the risks of metastasis were 6%, 48%, and 81% for radical prostatectomy with a Gleason score of 6, 7, and 8 to 10.

Eggener et al (2011) modeled clinical and pathologic data and follow-up information from 11,521 patients treated from 1987 to 2005 with radical prostatectomy at 4 academic centers to predict prostate cancer–specific mortality. They validated their model using 12,389 patients treated at a separate institution during the same period. The study reported that the 15-year prostate cancer–specific mortality rates stratified by patient age at diagnosis for pathologic Gleason score 6 or less, 3+4, 4+3, and 8 to 10 were 0.2% to 1.2%, 4.2% to 6.5%, 6.6% to 11% and 26% to 37%, respectively.

Therefore, given that the Gleason score is one of the most important factors predictive of prostate cancer and that there is consistent evidence supporting the superiority of MRI-targeted biopsy compared with TRUS-guided biopsy in terms of detecting clinically significant (Gleason score ≥7) prostate cancer, MRI-targeted biopsy is likely to identify patients with clinically significant cancer better, leading to changes in management that would be expected to improve survival, reduce morbidity and improve quality of life.

Summary: Magnetic Resonance Imaging‒Targeted Biopsy vs Standard Biopsy for Detecting Prostate Cancer
For individuals who have signs and symptoms of prostate cancer who receive MRI-targeted diagnostic biopsy of the prostate, the evidence includes numerous prospective and retrospective studies of paired cohorts, 2 randomized controlled trials, and systematic reviews and meta-analyses of these studies. These studies compare MRI-targeted biopsy with TRUS biopsy in detecting overall, clinically significant and clinically insignificant prostate cancers. Studies on the use of MRI-targeted prostate biopsy have shown that the technology may diagnose more clinically significant cancers than TRUS biopsy and fewer clinically insignificant cancers, which may stratify patients for treatment or for active surveillance.
Considering the prognostic value of risk stratification based on prostate biopsy, better diagnostic accuracy is likely to identify patients with clinically significant prostate cancer better leading to changes in management that would be expected to result in clinically meaningful improvement in outcomes (eg, survival or quality of life).

**MRI-Targeted Biopsy to ASSESS DISEASE PROGRESSION AMONG MEN UNDER Active Surveillance FOR PROSTATE CANCER**

**Clinical Context and Test Purpose**
The purpose of MRI-targeted prostate biopsy in patients on active surveillance for prostate cancer is to detect disease progression.

The question addressed in this evidence review is: Do MRI-targeted prostate biopsy techniques result in improved health outcome compared with 12-core TRUS-guided biopsy among prostate cancer patients under active surveillance?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest is men who are undergoing active surveillance for prostate cancer and are undergoing prostate biopsy to assess disease progression.

**Interventions**
The relevant interventions of interest are MRI-targeted prostate biopsy techniques: cognitive (or visual), MRI-in-bore, and MRI-TRUS fusion (visual targeted or software-based targeted).

**Comparators**
The following test is currently being used to make decisions about disease progression among patients under active surveillance: 12-core TRUS-guided prostate biopsy.

**Outcomes**
The general outcomes of interest are diagnostic accuracy (eg, test accuracy and validity) of clinically significant prostate cancer and health outcomes (eg, survival, quality of life).

Specifically, improving the detection rate of clinically significant prostate cancer and upgrading Gleason score are outcomes of primary interest because they would inform patient’s treatment plan and consequently impact health outcomes.

False-positive test results can lead to overdiagnosis and overtreatment, which exposes patients to potential morbidity of treatment without benefit.

False-negative test results can lead to failure to diagnose clinically significant cancers that require definitive treatment.
**Timing**
During active surveillance, a repeat biopsy of the prostate to detect disease progression among patients is usually conducted every 1 to 3 years. Among patients with no sign that the cancer has spread outside of the prostate, the relative 5-year survival rate is nearly 100% and, including all stages of prostate cancer, the relative 5-year survival rate is 99%, and the 15-year survival rate is 96%. Therefore, the timeframe for evaluation of survival in prostate cancer is approximately 10 to 20 years.

**Setting**
Prostate biopsy is generally done on an outpatient basis.

**Technical Performance**
Evidence on the technical performance of different MRI-targeted biopsy techniques have been discussed in the section on detection of prostate cancer.

**Diagnostic Accuracy**

**Systematic Reviews**
In 2015, Schoots et al conducted a systematic review (literature search through April 2014) of the use of MRI with men on active surveillance for prostate cancer.16 Reviewers assessed evidence for the use of MRI in men with low- or intermediate-risk prostate cancer diagnosed with TRUS-guided biopsy who were deemed suitable for active surveillance. Reviewers addressed 2 main clinical questions: (1) Can MRI detect clinically significant disease in men on active surveillance (thereby prompting treatment intervention rather than remaining on active surveillance)?; and (2) Can MRI be used in place of repeat standard TRUS biopsy to detect disease progression over time? The studies included reports on 3 distinct populations of men—group 1: men with histologic suitability for active surveillance who chose radical prostatectomy and had an MRI performed preoperatively (n=10 studies); group 2: men in active surveillance who had an MRI before a confirmatory biopsy (n=7 studies); and group 3: men in active surveillance assessed for disease progression on further MRI scans after an initial baseline scan (n=2 studies). The accuracy of MRI findings was assessed using whole-mount histology from post prostatectomy specimens (group 1), repeat standard biopsy (groups 2 and 3), or biopsies targeted to any suspicious lesions on MRI (groups 2 and 3). The MRI-targeted approach included in-bore targeting, visual registration, and software-assisted registration.

Ten publications have assessed radical prostatectomy data from men in active surveillance who had undergone preoperative MRI. Of men who chose surgery, 152 (14%) of 1070 were upstaged to T3 disease or worse, and 163 (43%) of 353 were upgraded to a Gleason score greater than 6. The likelihood of a positive MRI preoperatively was 73% (963/1326). Upgrading occurred in 43% (291/677) of cases with a positive preoperative MRI and in 27% (78/293) of men with a negative MRI preoperatively. (The denominators for these data differed because
not all groups included reported data for upgrading.) Upstaging occurred in 10% (54/557) of positive MRI cases and in 8% (16/194) with a negative MRI.

Seven studies assessed repeat biopsy data for men in active surveillance who had had a prior MRI (group 2). Four studies performed MRI-targeted biopsies plus TRUS-guided biopsies, and 3 studies only performed repeat standard (TRUS) biopsy following MRI. MRI-targeted biopsies were performed using software-registered MRI/US fusion in 2 of the 4 studies, visual registered (cognitive) MRI/US fusion in 1 study, and direct in-bore in 1 study. The likelihood of a positive MRI in men undergoing active surveillance and an MRI and repeat standard (TRUS) biopsy was 70% (340/488). Following a positive MRI, reclassification occurred in 39% (115/298) of those who underwent MRI-targeted repeat biopsy with TRUS and those who underwent TRUS only for repeat biopsy vs 17% (18/107) reclassification in patients with a negative MRI before repeat biopsy. In the cases with a positive MRI and MRI-targeted and TRUS biopsy, reclassification occurred in 47% (84/179) of cases.

Two studies included in the Schoots review assessed whether men in active surveillance could be evaluated for disease progression over time with MRI using repeat standard biopsy. The studies defined progression differently, and the criteria by which patients underwent repeat biopsy varied among study groups, making conclusions difficult.

**Randomized Controlled Trials**
There are no published RCTs comparing the evaluation of disease progression by MRI-targeted biopsy with systematic/TRUS-guided biopsy.

**Observational Studies**
Frye et al (2017) reported on a retrospective review among 166 men with prostate cancer in active surveillance for 2007 to 2015 in whom MRI-visible lesions were monitored by MRI-TRUS fusion biopsy. The study categorized patients into 2 groups: NIH low-risk (defined as International Society of Urological Pathology [ISUP] grade group 1) and NIH intermediate risk (ISUP grade group 2) (see Table 9). Pathologic disease progression was defined as any ISUP grade group 2 and 3 identified on surveillance biopsy in NIH low- and intermediate-risk groups, respectively. During a mean follow-up of 25.5 months, 49 (29.5%) patients had pathologic disease progression. MRI-targeted biopsy alone identified 22 (44.9%) of 49 patients who progressed compared with systematic biopsy alone, which identified 15 (30.6%) of 49 patients (p=0.03). The number needed to biopsy to detect 1 pathologic progression was 7.96 (215/27) for systematic biopsy and 3.14 (107/34) for MRI-targeted biopsy (p<0.001) (see Table 10).

Da Rosa et al (2015) conducted a prospective cohort study among 72 men with prostate cancer in active surveillance from 2011 to 2012 (see Table 9). The study reported that MRI-ultrasound fusion prostate biopsy showed a trend toward detecting more clinically significant cancers in active surveillance patients with substantially fewer cores compared with systematic biopsy (see Table 10). Additionally, MRI-TRUS fusion biopsy identified 3 Gleason score upgrades that
would not have been detected with systematic biopsy alone and upgraded a
Gleason score by 2 or more in 5 patients compared with 1 patient with systematic
biopsy. To avoid operator bias, the operator who performed systematic biopsy
following the MRI-TRUS fusion biopsy was blinded to the location of suspicious
lesions on MRI (see Table 10).

Ma et al (2017) reported on a single-center retrospective cohort study among 103
men with prostate cancer who were in active surveillance and underwent both
TRUS-guided prostate biopsy (systematic biopsy) and MRI-TRUS fusion.\(^\text{19}\) They
compared the detection rates for higher grade (Gleason score ≥7) prostate cancer
between these techniques (see Table 9). Of the 25 (24.3%) men in the cohort who
had higher grade cancer detected by either biopsy methods, 18 men were
detected by systematic biopsy only, 4 by MRI-TRUS fusion biopsy and 3 by both
(see Table 10). MRI-TRUS fusion biopsy alone had a lower sensitivity to detect
cancer with a Gleason score of 7 or higher compared with systematic biopsy
(relative sensitivity ratio, 0.33; 95% CI, 0.16 to 0.71). In the study, the urologists
were not blinded to the ROIs on mpMRI before the systematic biopsy, which might
have affected the higher efficiency systematic biopsy if the operator targeted areas
where an ROI was identified on mpMRI. Additionally, not blinding the radiologists
to previous systematic biopsy findings also might have affected the higher grade
cancer detections in this cohort.

Walton Diaz et al (2015) evaluated the performance of mpMRI and MRI-TRUS
fusion biopsy for monitoring patients with prostate cancer (n=58) in active
surveillance (see Table 9).\(^\text{20}\) The study reported a higher detection rates for
disease progression by MRI-TRUS fusion biopsy than by systematic biopsy (see
Table 10). The number needed to biopsy to detect a single Gleason grade
progression was 8.74 (70/8) for systematic biopsy vs 2.9 (26/9) for MRI-TRUS
fusion biopsy (p<0.02).

Table 9. Summary of Study Characteristics of Key Observational Studies
Comparing Subjects Receiving Both MRI-Targeted and MRI-TRUS Fusion
Biopsy

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study Type</th>
<th>Location</th>
<th>Dates</th>
<th>MRI-Targeted Biopsy</th>
<th>MRI-TRUS Fusion Biopsy</th>
<th>Median FU, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frye et al</td>
<td>2017(^\text{17})</td>
<td>Paired retrospective cohort</td>
<td>U.S.</td>
<td>2007-2015</td>
<td>166</td>
<td>166</td>
<td>25.5</td>
</tr>
<tr>
<td>Da Rosa et al</td>
<td>2015(^\text{18})</td>
<td>Prospective cohort</td>
<td>Canada</td>
<td>2011-2012</td>
<td>72</td>
<td>72</td>
<td>38</td>
</tr>
<tr>
<td>Ma et al</td>
<td>2017(^\text{19})</td>
<td>Paired retrospective cohort</td>
<td>U.S.</td>
<td>2014-2015</td>
<td>103</td>
<td>103</td>
<td>60</td>
</tr>
<tr>
<td>Walton Diaz et</td>
<td>2015(^\text{20})</td>
<td>Paired retrospective cohort</td>
<td></td>
<td>2007-2014</td>
<td>58</td>
<td>58</td>
<td>16.1</td>
</tr>
</tbody>
</table>

FU: follow-up; mpMRI: multiparametric magnetic resonance imaging; MRI: magnetic resonance imaging; TRUS: transrectal ultrasound.
\(^\text{a}\) Study population includes only men with lesions identified on mpMRI.
**Section Summary: Diagnostic Accuracy**

The evidence for the use of MRI-targeted surveillance prostate biopsy includes prospective and retrospective studies of paired cohorts and a systematic review. Recent studies conducted among men with prostate cancer who are in active surveillance have generally shown a pattern of greater detection of pathologic disease progression using MRI-TRUS fusion biopsy than systematic biopsy. However, the studies often have small sample sizes and lack the statistical power to detect significant differences. Considering the clinical similarities in the goals of biopsy during initial diagnosis and follow-up biopsy for patients in active surveillance (ie, detecting clinically significant cancer and risk stratification of prostate cancer cases) and evidence of the superiority of MRI-targeted biopsy over TRUS biopsy in detecting clinically significant prostate cancer among biopsy-naive and previously biopsy-negative men, the diagnostic performance of MRI-TRUS could be expected to be similar among men on active surveillance.

**Table 10. Summary of Key Observational Studies Comparing Subjects Receiving Both MRI-Targeted and MRI-TRUS Fusion Biopsy**

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Diagnostic Yield With GS Upgrading</th>
<th>GS ≥7 Cancer Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Comparators</td>
<td>Outcome Rate</td>
</tr>
<tr>
<td></td>
<td>MRI-TRUS fusion only</td>
<td>44.9% (22/49)</td>
</tr>
<tr>
<td>Frye et al (2017)</td>
<td>Systematic TRUS only</td>
<td>30.6% (15/49)</td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>24.5% (12/49)</td>
</tr>
<tr>
<td>Da Rosa et al (2015)</td>
<td>MRI-TRUS fusion</td>
<td>87% (13/15)</td>
</tr>
<tr>
<td></td>
<td>Systematic</td>
<td>67% (10/15)</td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>53% (10/19)</td>
</tr>
<tr>
<td>Ma et al (2017)</td>
<td>MRI-TRUS fusion</td>
<td>6.8% (7/103)</td>
</tr>
<tr>
<td>Walton Diaz et al (2015)</td>
<td>MRI-TRUS fusion</td>
<td>53% (9/17)</td>
</tr>
<tr>
<td></td>
<td>Systematic</td>
<td>35% (6/17)</td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>12% (2/17)</td>
</tr>
</tbody>
</table>

GS: Gleason score; HR: hazard ratio; MRI: magnetic resonance imaging; RR: relative risk; TRUS: transrectal ultrasound.

* Study population includes only men with lesions identified on multiparametric MRI.

* Reference is pathologic progression/GS ≥7 cases detected by either method or by 2 methods combined.

**Clinical Utility**

Currently, there is no direct evidence from studies demonstrating that MRI-targeted prostate biopsies result in improved patient outcomes (eg, survival or quality of life) among prostate cancer patients who are in active surveillance. For
patients in active surveillance, physicians use the Gleason score of the biopsied tumors to determine whether there is a need to start definitive prostate cancer therapy. An increase in Gleason score to 7 or higher is one of the parameters used in recommending definitive therapy in this population.

Klotz et al (2015) conducted a single-center prospective single-arm cohort study to describe the long-term outcomes of an active surveillance protocol among 993 men with favorable-risk prostate cancer.24 All 15 patients who died of prostate cancer had confirmed metastases before death. An additional 13 (1.3%) patients with confirmed metastases are alive (n=9) or died of other causes (n=4). Only two of 28 patients who developed metastases were not upgraded to Gleason score of 7 or higher before developing metastatic disease. The finding of a Gleason score of 8 to 10 on confirmatory biopsy was associated with early progression to metastasis (Gleason score of 6 vs 8, p=0.034; Gleason score of 7 vs 8, p=0.023). Moreover, as described above in our discussion of the clinical utility of MRI-targeted biopsy among biopsy-naive or previously biopsy-negative populations, there is evidence in favor of the prognostic value of Gleason score based on prostate biopsy.

Because detection of clinically significant cancer is the parameter of definitive therapy and a high Gleason score is a predictor of metastatic disease, higher detection rates of pathologic disease progression (Gleason score upgrading) and cancer with a Gleason score 7 or higher by MRI-targeted biopsy compared with TRUS biopsy is likely to permit physicians to make better informed decisions for definitive treatment of prostate cancer which would eventually improve survival, reduce morbidity and improve quality of life.

**Summary: MRI-Targeted Biopsy to Assess Disease Progression Among Men Under Active Surveillance for Prostate Cancer**

For individuals who have prostate cancer, are in active surveillance, and have received MRI-targeted biopsy, the evidence includes a systematic review and observational studies of paired cohorts comparing MRI-targeted biopsy with TRUS biopsy for detecting pathologic progression of prostate cancer in terms of Gleason score and detection of higher grade (Gleason score ≥7) cancer. Current evidence would suggest that, compared with TRUS biopsy, MRI-targeted biopsy is better in detecting patients in active surveillance who have progressed and need definitive intervention. With the greater ability to detect prostate cancer with a Gleason score of 7 or higher, which is a critical parameter for guiding definitive therapy in prostate cancer, use of this technique is likely to improve clinically meaningful outcomes (eg, survival or quality of life) in this population.

**Summary of Evidence**

For individuals who have suspicion of prostate cancer who receive MRI-targeted biopsy, the evidence includes numerous prospective and retrospective studies of paired cohorts, 2 randomized controlled trials and systematic reviews and meta-analyses of these studies comparing MRI-targeted biopsy with TRUS-guided biopsy in detecting overall, clinically significant and clinically insignificant prostate cancers. Relevant outcomes are overall survival, disease-specific survival, test accuracy, morbid events, and quality of life. Studies on the use of MRI-targeted
prostate biopsy have shown that the technology may diagnose more clinically significant cancers than TRUS biopsy and fewer clinically insignificant cancers, which might stratify patients for treatment and active surveillance. Considering the prognostic value of risk stratification based on prostate biopsy, better diagnostic accuracy is likely to identify patients more accurately with clinically significant prostate cancer leading to changes in management that would be expected to result in clinically meaningful outcomes in terms of survival or quality of life. The evidence is sufficient to determine that the technology results in a meaningful improvement in net health outcome.

For individuals who have prostate cancer and in active surveillance who receive MRI-targeted biopsy, the evidence includes a systematic review and observational studies of paired cohorts comparing MRI-targeted biopsy with TRUS biopsy in detecting pathologic progression of prostate cancer in terms of Gleason score and detection of higher grade (Gleason score ≥7) cancer. Relevant outcomes are overall survival, disease-specific survival, test accuracy, morbid events, and quality of life. Current evidence has suggested that, compared with TRUS biopsy, MRI-targeted biopsy is better at detecting those patients in active surveillance who have progressed and need definitive intervention. With the greater ability to detect prostate cancer with a Gleason score 7 or higher, which is a critical parameter for definitive therapy in prostate cancer, use of this biopsy guidance technique is likely to translate into positive clinically meaningful outcomes (eg, survival and quality of life) in this population. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Supplemental Information**

**Practice Guidelines and Position Statements**

**National Comprehensive Cancer Network**
National Comprehensive Cancer Network guidelines\(^22\) (v.1.2017) on prostate cancer early detection make the following statement on the use of multiparametric magnetic resonance imaging (MRI) in the staging of prostate cancer:

> “Emerging data suggest that, in men undergoing initial biopsy, targeting using MRI/ultrasound fusion may significantly increase the detection of clinically significant, higher-risk (Gleason grade ≥4+3=7) disease while lowering the detection of lower-risk (Gleason sum 6 or lower-volume Gleason grade 3+4=7) disease.”

Regarding use of MRI transrectal ultrasound (TRUS) fusion biopsy among patients in active surveillance National Comprehensive Cancer Network guidelines mention that MRI-TRUS fusion biopsy may improve the detection of higher grade (Gleason score ≥7) cancers.

**American College of Radiology**
The American College of Radiology has issued appropriateness criteria (last reviewed in 2016) that stated\(^23\):
“MRI-targeted biopsy of the prostate ... promises to dramatically alter the current approach to prostate cancer diagnosis. MRI-guided biopsy may be used for baseline diagnosis in patients who are biopsy naïve, for diagnosis of cancer (often in the central gland) in patients who have had a negative TRUS-guided systematic biopsy but who continue to have an elevated PSA [prostate-specific antigen] or other cause for clinical concern, for re-evaluation of tumor grade in patients on active surveillance, and for diagnosis of local recurrence in patients who have undergone prior therapy.”

**National Institute for Health and Care Excellence**
The 2014 National Institute for Health and Care Excellence guidance on the diagnosis and treatment of prostate cancer has recommended considering multiparametric MRI (using T2- and diffusion-weighted imaging) for men with a negative TRUS 10- or 12-core biopsy to determine whether another biopsy is needed. Another biopsy should not be offered if the multiparametric MRI is negative unless additional risk factors are present.

**American Urological Association and Society of Abdominal Radiology**
The American Urological Association Society of Abdominal Radiology published joint guidelines in 2016 on prostate MRI and MRI-targeted biopsy for patients with prior negative biopsy. The Association recommended:

“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 in any patient with a prior negative biopsy who has persistent clinical suspicion for prostate cancer and who is undergoing a repeat biopsy.”

**U.S. Preventive Services Task Force Recommendations**
No U.S. Preventive Services Task Force recommendations for MRI-targeted or MRI/ultrasound fusion biopsy of the prostate have been identified.

**Medicare National Coverage**
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might influence this policy are listed in Table 11.

**Table 11. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT</td>
<td>Title</td>
<td>Subjects</td>
<td>Date</td>
</tr>
<tr>
<td>-------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>NCT02242773</td>
<td>MRI-Guided Biopsy Selection of Prostate Cancer Patients for Active Surveillance Versus Treatment: The Miami MAST Trial</td>
<td>165</td>
<td>Oct 2017</td>
</tr>
<tr>
<td>NCT02380027</td>
<td>Prostate Evaluation for Clinically Important Disease: Sampling Using Image-guidance Or Not? (PRECISION)</td>
<td>470</td>
<td>Oct 2017</td>
</tr>
<tr>
<td>NCT00775866</td>
<td>MRI-Guided Biopsy for Suspicion of Locally Recurrent Prostate Cancer After External Beam Radiotherapy</td>
<td>90</td>
<td>Nov 2017</td>
</tr>
<tr>
<td>NCT01883128</td>
<td>An Evaluation of a Novel Imaging Based Complex Diagnostic and Therapeutic Pathway Intervention for Men Who Fail Radiotherapy for Prostate Cancer</td>
<td>177</td>
<td>Oct 2019</td>
</tr>
<tr>
<td>NCT02138760</td>
<td>Comparison of MRI Fusion Biopsy Techniques in Men With Elevated PSA and Prior Negative Prostate Biopsy</td>
<td>400</td>
<td>Dec 2015</td>
</tr>
<tr>
<td>(unknown)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02564549</td>
<td>MRI-Based Active Surveillance to Avoid the Risks of Serial Biopsies in Men With Low-Risk Prostate Ca</td>
<td>192</td>
<td>Oct 2017</td>
</tr>
<tr>
<td>(suspended)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

References


Billing Coding/Physician Documentation Information

55700 Biopsy, prostate; needle or punch, single or multiple, any approach
55705 Biopsy, prostate; incisional, any approach
55706 Biopsies, prostate, needle, transperineal, stereotactic template guided saturation sampling, including imaging guidance
76498 Unlisted magnetic resonance procedure (eg, diagnostic, interventional)
76942 Ultrasonic guidance for needle placement (eg, biopsy, aspiration, injection, localization device), imaging supervision and interpretation
77021 Magnetic resonance guidance for needle placement (eg, for biopsy,
needle aspiration, injection, or placement of localization device
radiological supervision and interpretation

**ICD-10 Codes**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C61</td>
<td>Malignant neoplasm of prostate</td>
</tr>
<tr>
<td>D07.5</td>
<td>Carcinoma in situ of prostate</td>
</tr>
<tr>
<td>D40.0</td>
<td>Neoplasm of uncertain behavior of prostate</td>
</tr>
</tbody>
</table>

**Additional Policy Key Words**

N/A

**Policy Implementation/Update Information**

- **3/2017** New Policy. Considered investigational.
- **10/17** The policy statement was changed to “Magnetic resonance imaging‒targeted biopsy of the prostate may be considered to be medically necessary for diagnosis and active surveillance of prostate cancer.”

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.