7.01.152	Magnetic Resonance Imaging–Targeted Biopsy of the Prostate		
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Section:	7.0 Surgery	**Page:**	Page 1 of 23

Policy Statement

Magnetic resonance imaging–targeted biopsy of the prostate may be considered **medically necessary** for diagnosis and active surveillance of prostate cancer**.**

Policy Guidelines

Coding
There is no specific CPT code for this procedure.

This procedure would likely be reported with the following prostate biopsy code:

- **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

It would also likely be reported with the following MRI guidance code:

- **77021**: Magnetic resonance guidance for needle placement (e.g., for biopsy, needle aspiration, injection, or placement of localization device) radiological supervision and interpretation

Description

Before a transrectal ultrasound-guided biopsy, a magnetic resonance imaging (MRI) scan can be used to pinpoint the location of suspicious lesions 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 not needing treatment. In accomplishing the secondary function, patients are placed into 1 of 2 categories: those only needing active surveillance; and those needing definitive intervention.

Related Policies

- Focal Treatments for Prostate Cancer
- Saturation Biopsy for Diagnosis, Staging, and Management of Prostate Cancer

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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 the FDA through the 510(k) process. Fusion software includes Artemis™ (Eigen), BioJet™ (D&K Technologies), BiopSee® (MedCom), Real-time Visual Sonography (Hitachi, Tokyo, Japan), UroNav™ (Invivo/Philips), Urostation® (Koelis), and Virtual Navigator (Esaote).

Rationale

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]

Diagnosis

The diagnosis and grading of prostate cancer are performed by taking a biopsy of the prostate gland. A prostate biopsy typically is performed in men who have an elevated prostate-specific antigen 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 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 prostate-specific antigen, 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

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.[2] 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 tumors 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 (i.e., 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 intraprocedural (real-time) ultrasound to direct the biopsy needle to an ultrasound region of interest defined by multiparametric MRI.

Table 1 summarizes the MRI requirements for the 3 different MRI-guided prostate biopsy techniques described.

Table 1. Techniques for MRI-Guided Prostate Biopsy

Method	MRI Requirement(s)	Description
Visual	• Prior MRI of prostate lesion	US operator targets the biopsy needle at the area of the prostate where prior MRI indicated a lesion during TRUS
Direct	• Prior MRI of prostate lesion • Contemporaneous MR images of biopsy needle in prostate lesion location	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

Method	MRI Requirement(s)	Description
MRI-US fusion (visual targeted or software-based targeted)	• Prior MRI of prostate lesion • Overlay of prior MR image over real-time US	Prior MR image superimposed over an intraprocedure (real-time) US to direct the biopsy needle during TRUS

MR: magnetic resonance; MRI: magnetic resonance imaging; TRUS: transrectal ultrasound; US: ultrasound.

Currently, there is evidence comparing these 3 techniques in terms of their ability to detect overall or clinically significant prostate cancer.

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 prostate-specific antigen 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.

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

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 population of interest is 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 (i.e., test accuracy and validity) of clinically significant prostate cancer and health outcomes (i.e., survival, quality of life).

Specific outcomes are improving the detection of clinically significant prostate cancer; increasing accurate risk stratification; and reducing the overdiagnosis of indolent tumors requiring only active surveillance. These are outcomes of primary interest because they would inform the 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 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 the evaluation of survival in prostate cancer is approximately 10 to 20 years.

Setting
Prostate biopsy is generally administered in an outpatient setting by urologists.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews
Tang et al (2018) published a systematic review and meta-analysis of 13 cohorts (12 studies; total N=3225 patients) of men undergoing a biopsy after previous negative biopsy or initial biopsy for suspected prostate cancer.[3] The primary outcome was prostate cancer detection rate of MRI-TRUS fusion-guided targeted biopsy compared with the detection rate of TRUS-guided biopsy. The MRI-TRUS fusion biopsy detected prostate cancer in 52.7% (n=1698) of the entire cohort, significantly more than the 42.6% (n=1375) detected by the TRUS biopsy alone ($p<0.05$). Reviewers also took into account whether cohorts included patients with initial biopsy (5 cohorts; n=1823 patients), a previous negative biopsy (3 cohorts; n=528 patients), or either (5 cohorts; n=874 patients). In patients with initial biopsy, MRI-TRUS fusion biopsy had a detection rate of 56.1% (n=1023 patients), and TRUS biopsy alone had a detection rate of 48.1% (n=877 patients). In patients with a previous negative biopsy, detection rates were higher for the MRI-TRUS fusion biopsy (32.8%) than for TRUS biopsy alone $p<0.05$). Direct comparison of the 2 biopsy methods did not identify significantly different detection rates for the entire cohort; however, subgroup analysis of higher Gleason score disease and lower Gleason score disease revealed that MRI-TRUS fusion biopsy was significantly superior at detecting higher Gleason score disease in patients with previous negative biopsy ($p<0.05$). The subgroup analyses (10 studies; n=2573 patients) also found that MRI-TRUS fusion biopsy identified fewer cases of lower Gleason score disease (12.9%) than was identified by TRUS biopsy (45.58%; $p<0.05$). Reviewers noted that, while there was no evidence of publication bias or significant selection bias, some of the studies inconsistently reported blinding, and 10 studies came from the same center.

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.[4] 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%) and TRUS-guided biopsy (sensitivity, 83%) for overall prostate cancer detection. MRI-targeted biopsy (sensitivity, 90%) had higher sensitivity to detect clinically significant prostate cancer than TRUS-guided biopsy (sensitivity, 79%). MRI-targeted biopsy (sensitivity, 7%) had lower sensitivity to detect clinically insignificant prostate cancer than TRUS-guided biopsy (sensitivity, 14%).

Wu et al (2015) published a meta-analysis (literature search through May 2015) to determine whether MRI-TRUS fusion biopsy is better than standard systematic biopsy in detecting prostate cancer.[5] In 16 trials (1 randomized controlled trial [RCT], 15 paired cohort studies), a total of 3105 participants underwent MRI-TRUS fusion or TRUS-guided biopsy (see Table 2). Reviewers evaluated the quality of each trial using the Quality Assessment Tool for Diagnostic Accuracy Studies. While there was variation in the methodologic quality of selected studies, none was 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 3 and 4). 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) compared with that of TRUS-guided biopsy (30% [786/2583] men), with no heterogeneity between trials. MRI-TRUS fusion biopsy (255 [11%] of 2395 men) had a lower detection rate of clinically insignificant prostate cancer compared with TRUS-guided systematic biopsy (15% [368/2494] men).

A systematic review and meta-analysis by Schoots et al (2015), which searched the literature 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 2).[6] Selected studies included men with suspected prostate cancer scheduled for transrectal biopsy because of increased PSA levels and/or positive digital rectal exam. Overall, based on the Quality Assessment Tool for Diagnostic Accuracy Studies 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 1 indicated that MRI-targeted biopsy detected more cancers than TRUS-guided biopsy, and a relative sensitivity less than 1 indicated that MRI-targeted biopsy detected fewer cancers than TRUS-guided biopsy. Analyses were performed for 2 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% confidence interval [CI], 80% to 89%] vs sensitivity, 81% [95% CI, 70% to 88%], respectively; see Tables 3 and 4). Ten studies presented data on the rates of detection of significant vs insignificant prostate cancer. Of the 10 studies, 5 reported on results of 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% vs sensitivity, 76%) and a lower rate of detection of insignificant prostate cancer (sensitivity, 44% vs sensitivity, 83%), 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]).

Appendix Table 1 provides a crosswalk for all studies included in some of the systematic reviews assessed in this section.

Table 2. Characteristics of Systematic Reviews Assessing Prostate Cancer Detection Rates for MRI-Targeted and TRUS-Guided Biopsies

Study	Dates	Trials	N (Range)	Design
Wegelin et al (2017)[4]	To Oct 2014	25	3520 (20-1003)	Paired cohort (sequential sampling for 2 biopsy techniques in same individual)
Wu et al (2015)[5]	To May 2015	16	3105 (30-1003)	1 RCT, 15 cohort studies
Schoots et al (2015)[6]	To May 2014	16	1926 (32-582)	Paired cohort (sequential sampling for 2 biopsy techniques in same individual)

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

Table 3. Systematic Review Results (Relative Risk, Relative Sensitivity) of Prostate Cancer Detection for MRI-Targeted and TRUS-Guided Biopsies

Study	Trials	n/N	Outcome: Detection Rates	RR/RS	95% CI	p	I^2, %
Wegelin et al (2017)[4]	25	3520	Prostate cancer	0.98	0.90 to 1.07		
	14	2328	Clinically significant prostate cancer	1.16	1.02 to 1.32		
	14	2328	Clinically insignificant prostate cancer	0.47	0.35 to 0.63		
Wu et al (2015)[5]	16	3013/3015	Prostate cancer	1.06	1.01 to 1.12	0.03	28
	10	2481/2583	Clinically significant prostate cancer	1.19	1.10 to 1.29	<0.01	0
	10	2395/2494	Clinically insignificant prostate cancer	0.68	0.59 to 0.79	<0.01	72
Schoots et al (2015)[6]	16	1926	Prostate cancer	1.05	0.94 to 1.19		88
	10	1657	Clinically significant prostate cancer	1.20	1.09 to 1.32		68
	10	1657	Clinically insignificant prostate cancer	0.56	0.37 to 0.85		78

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

Table 4. Systematic Review Results of Prostate Cancer Detection Rates for MRI-Targeted and TRUS-Guided Biopsies

Study	Sensitivity (95% CI), %, or Cancer Detection Rate, n/N		Trials	Measure	Estimate	95% CI	p	I^2, %
	MRI-Targeted Biopsy	Systematic Biopsy						
Wegelin et al (2017)[4]	81 (76 to 85)	83 (77 to 88)	25	Relative sensitivity	0.98	0.90 to 1.07		
	90 (85 to 94)	79 (68 to 87)	14	Relative sensitivity	1.16	1.02 to 1.32		
	7 (4 to 10)	14 (11 to 18)	14	Relative sensitivity	0.47	0.35 to 0.63		
Wu et al (2015)[5]	1412/3103	1373/3105	16	Relative risk	1.06	1.01 to 1.12	0.03	28
	892/2481	786/2583	10	Relative risk	1.19	1.10 to 1.29	<0.01	0
	255/2395	368/2494	10	Relative risk	0.68	0.59 to 0.79	<0.01	72
Schoots et al (2015)[6]	85 (80 to 89)	81 (70 to 88)	16	Relative sensitivity	1.05	0.94 to 1.19		88
	91 (87 to 94)	76 (64 to 84)	10	Relative sensitivity	1.20	1.09 to 1.32		68
	44 (26 to 64)	83 (77 to 87)	10	Relative sensitivity	0.56	0.37 to 0.85		78

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

Subsection Summary: Systematic Reviews

Systematic reviews and meta-analyses of observational studies have consistently reported the superior sensitivity of the MRI-targeted biopsy techniques in detecting clinically significant prostate cancer compared with TRUS-guided biopsy.

Randomized Controlled Trials

Kasivisvanathan et al (2018) published a multicenter noninferiority trial of 500 men with suspicion of prostate cancer who were randomized to MRI-targeted biopsy (n=252) or standard TRUS-guided biopsy (n=248).[7] Those whose MRI results did not suggest prostate cancer (71 [28%] patients) did not receive a biopsy. A greater proportion of patients in the MRI-targeted biopsy group were diagnosed with clinically significant disease (95 [38%] patients) than in the standard biopsy group (64 [26%] patients): the adjusted difference between groups was 12 percentage points (95% CI, 4% to 20%; p=0.005). There were also fewer diagnoses of clinically insignificant cancer in the MRI-targeted biopsy group (23 [9%] patients) than in the standard biopsy group (55 [22%] patients), which may indicate a reduction in overtreatment. While there were some limitations, including the level of agreement between the multiparametric MRI (mpMRI) site and central radiologist reading (78%), overall MRI-targeted biopsy proved to be not only noninferior to standard TRUS-guided biopsy but superior for men who suspected prostate cancer but not had a previous biopsy.

Porpiglia et al (2017) published a single-center RCT in Italy evaluating 212 biopsy-naive patients with suspected prostate cancer (PSA level ≤15 ng/mL and negative digital rectal examination results).[8] Patients were randomized to a prebiopsy mpMRI group (n=107) or a standard biopsy group (n=105) (see Table 5). 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 the 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 patient assignment and mpMRI results. In the intention-to-treat analysis, the detection rate was higher in the mpMRI group than in the standard biopsy group for overall prostate cancer and for clinically significant prostate cancer (see Table 6). 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).

Baco et al (2016) 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 (n=89; 2 targeted biopsy from palpable lesions followed by 12-core systematic random biopsy) to compare detection rates for overall and clinically significant prostate cancers (see Table 5).[9] 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 differ significantly between MRI-TRUS fusion biopsy and control groups (see Table 6). Similarly, for detection of clinically significant cancer in 66 MRI-targeted biopsy patients vs 60 random biopsy only control patients with normal digital rectal exam results, there was no significant difference in detection rates (21% vs 25%, respectively, p=0.7).

Table 5. Summary of Randomized Controlled Trial Characteristics for Prostate Cancer Detection Rates between MRI-Targeted and TRUS-Guided Biopsies

Study	Countries	Sites	Dates	Population	Interventions	
					MRI-TRUS Fusion Biopsy	Standard Biopsy
Porpiglia et al (2017)[8]	Italy	1	2014-2016	Biopsy-naive men with PSA ≤15 ng/mL and negative DRE	107 (81 targeted biopsy, 26 standard biopsy)	105
Baco et al (2016)[9]	Norway	1	2011-2013	Biopsy-naive men with PSA 4-20 ng/mL and/or abnormal DRE	86	89

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

Table 6. Summary of Randomized Controlled Trial Results for Prostate Cancer Detection Rates between MRI-Targeted and TRUS-Guided Biopsies

Study	Primary Outcome	Biopsy Results, % (n/N)		
		MRI-Targeted	TRUS-Guided	p
Porpiglia et al (2017)[8]	Overall prostate cancer detection	43.9 (47/107)	18.1 (19/105)	<0.001
	Clinically significant prostate cancer detection	50.5 (54/107)	29.5 (31/105)	0.002
Baco et al (2016)[9]	Overall prostate cancer detection	59 (51/86)	54 (48/89)	0.4
	Clinically significant prostate cancer detection	44 (38/86)	49 (44/89)	0.5

MRI: magnetic resonance imaging; TRUS: transrectal ultrasound.

Subsection Summary: Randomized Controlled Trials

While the Porpiglia et al (2017) RCT demonstrated the superiority of MRI-targeted biopsy in detecting overall and clinically significant prostate cancer, the Baco et al (2016) RCT did not find a significant difference between these techniques. Studies have suggested that MRI using endorectal coils provide superior spatial resolution and superior sensitivity to detect prostate cancer compared with MRI not using endorectal coils,[10,11] which might explain the failure of the Baco et al (2016) trial to demonstrate the superiority of MRI-targeted biopsy in detecting clinically significant cancer compared TRUS biopsy among patients suspicious for prostate cancer with normal digital rectal exam results.

Observational Studies

Maxeiner et al (2018) retrospectively analyzed results from 318 biopsy-naive consecutive patients who underwent mpMRI and subsequent MRI-TRUS fusion-guided targeted biopsy and TRUS biopsy.[12] Results from targeted biopsy alone detected cancer in 67% (n=213) patients, and TRUS biopsy alone detected cancer in 70% (n=222) of patients. According to the Prostate Imaging Reporting and Data System (PI-RADS), 55 patients had a score of 3, of whom 21 (38%) had detectable cancer; 154 had a score of 4, of whom 120 (78%) had cancer; and 109 had a score of 5, of whom 104 (95%) had cancer detected by 1 or both biopsy methods. Of the cancerous lesions detected by MRI-TRUS fusion targeted biopsy and TRUS biopsy, the prostate tumors were deemed to be clinically significant (Gleason score ≥4+3=7) in 195 (61%) of the entire cohort. Diagnoses of insignificant cancer were identical for MRI-TRUS fusion plus TRUS (16%), but the combination of targeted biopsy and TRUS biopsy showed an improvement in detection of 10% over that detected by targeted biopsy alone, which only detected significant cancer in 163 (51%) of patients. Study limitations included the single-center, nonrandomized design, and a different definition of clinically significant prostate disease in relation to previous studies. Based on their observations of the biopsy-naive cohort, authors concluded that targeted biopsy combined with systematic biopsy improved diagnostic accuracy considerably compared with targeted biopsy alone.

Filson et al (2016) reported a single-center prospective study evaluating 1042 men with (1) an elevated PSA level or abnormal digital rectal examination result, or (2) confirmation of low-risk prostate cancer for patients considering active surveillance.[13] 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 7). Among 825 patients with 1 or more ROI of grade 3 or higher, a 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 8).

Siddiqui et al (2015) reported on a single-center prospective cohort study of 1003 men with elevated PSA levels or abnormal digital rectal exam results undergoing both MRI-TRUS fusion biopsy and standard biopsy concurrently from 2007 through 2014 (see Table 7).[14] 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) cancers (213 cases vs 258 cases, p<0.001) (see Table 8), 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. The sensitivity rates to detect intermediate- to high-risk prostate cancer using MRI-targeted, TRUS, and MRI-TRUS fusion biopsy were 77%, 53%, and 85%, respectively (see Table 9). Accuracy rates to detect intermediate- to high-risk prostate cancer using MRI-targeted standard and combined biopsy were 73%, 59%, and 69%, 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, TRUS biopsy alone, and MRI-TRUS fusion biopsy. The benefit was defined as a surgical intervention limited to intermediate- and high-risk tumors, while harm was a surgical procedure for low-risk tumors. The area under the curve (or net benefit) was highest for MRI-targeted biopsy (0.73). The areas under the curve for TRUS biopsy and MRI-TRUS fusion biopsy were 0.59 and 0.67, respectively (p<0.05 for all comparisons; see Table 9).

Table 7. Observational Study Characteristics for Prostate Cancer Detection Rates for MRI-Targeted and TRUS-Guided Biopsies

Study	Type	Country	Dates	MRI-TRUS Fusion Biopsy	Standard Biopsy
Filson et al (2016)[13]	Prospective	U.S.	2009-2014	825	825
Siddiqui et al (2015)[14]	Prospective	U.S.	2007-2014	1003	1003

MRI: magnetic resonance imaging; TRUS: transrectal ultrasound.

Table 8. Summary of Observational Study Results for Prostate Cancer Detection Rates for MRI-Targeted and TRUS-Guided Biopsies

Study	High-Risk/Clinically Significant Prostate Cancer			Overall Prostate Cancer	
	Comparators	Detection Rate, % (n/N)	p	Comparators	Detection Rate, % (n/N)
Filson et al (2016)[13]	MRI-TRUS fusion only	28 (229/825)[b]		MRI-TRUS fusion	44 (360/825)
	Artemis-guided systematic only	24 (199/825)[b]	<0.001	Systematic	49 (307/825)
	Combined	35 (289/825)[b]		Combined	60 (493/825)
Siddiqui et al (2015)[14]	MRI-TRUS fusion	17 (173/1003)[a]	<0.001	MRI-TRUS fusion	46 (461/1003)
	TRUS-guided systematic	12 (122/1003)[a]		TRUS-guided	47 (469/1003)

MRI: magnetic resonance imaging; RR: relative risk; TRUS: transrectal ultrasound.
[a] High-risk (Gleason score≥4+3) cancer detection rate.
[b] Clinically significant (Gleason score ≥7, both ≥4+3 or ≥3+4) cancer detection rate.

Table 9. Results of Different Biopsy Approaches in Detecting Intermediate- to High-Risk Prostate Cancer on Whole Gland Prostatectomy Specimen

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

Adapted from Siddiqui et al (2015).[14]
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 detection of 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: Clinically Valid
Multiple systematic reviews and meta-analyses of paired cohort studies have consistently reported the superiority of MRI-targeted biopsy over the 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 that MRI-targeted biopsy had a better detection rate for clinically significant prostate cancer. In the other RCT, Baco et al (2016) 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) contributed the superior test validity and higher net benefit of using MRI-targeted than TRUS 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.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Currently, no direct evidence from studies has demonstrated that MRI-targeted prostate biopsies result in improved patient outcomes (e.g., survival, quality of life).

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

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 analysis using the Johns Hopkins Radical Prostatectomy Database to examine the correlation between Gleason score and

pathologic stage and biochemical recurrence in 6462 men.[15] Almost 95% of patients with cancer and 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 a Gleason score of 3+4=7 on biopsy had an estimated 5-year biochemical recurrence-free survival rate of 83%.

Antonarakis et al (2012) retrospectively analyzed 450 men who underwent prostatectomy and subsequently developed PSA recurrence (≥0.2 ng/mL) to assess the metastasis-free survival and define clinical prognostic factors modifying metastasis risk.[16] 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 data from 11,521 patients treated from 1987 to 2005 with radical prostatectomy at 4 academic centers to predict prostate cancer–specific mortality.[17] 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 an important factor 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.

Section Summary: Detection of Prostate Cancer
For individuals who have signs and symptoms of prostate cancer who receive a diagnostic MRI-targeted biopsy of the prostate, the evidence includes numerous prospective and retrospective studies of paired cohorts, 2 RCTs, 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 (e.g., survival or quality of life).

Disease Progression during Active Surveillance
Clinical Context and Test Purpose
The purpose of MRI-targeted prostate biopsy in patients on active surveillance for prostate cancer recurrence 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 recurrence and are undergoing prostate biopsy to detect 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 monitoring for cancer progression among men under active surveillance: 12-core TRUS-guided prostate biopsy.

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

Specifically, improving the detection rate of clinically significant prostate cancer and upgrading the Gleason score are outcomes of primary interest because they would inform the 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 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 the evaluation of survival in prostate cancer is approximately 10 to 20 years.

Setting
Prostate biopsy is generally administered in an outpatient setting by urologists.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews
Schoots et al (2015) conducted a systematic review (literature search through April 2014) of MRI-targeted biopsy with men on active surveillance for prostate cancer.[18] 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-targeted biopsy detect clinically significant disease in men on active surveillance (thereby prompting treatment intervention rather than remaining on active surveillance)?; and (2) Can MRI-targeted biopsy 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-targeted biopsy 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-targeted biopsy 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 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-TRUS fusion in 2 of the 4 studies, visual registered (cognitive) MRI-TRUS 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 repeat MRI-TRUS targeted biopsy and those who underwent repeat TRUS biopsy only vs 17% (18/107) reclassification in patients with a negative MRI before repeat biopsy. In the cases with a positive MRI and MRI-TRUS biopsy, reclassification occurred in 47% (84/179) of cases.

Two studies included in the Schoots et al (2015) 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 TRUS-guided biopsy.

Observational Studies

Frye et al (2017) reported on a retrospective review of 166 men with prostate cancer in active surveillance from 2007 to 2015 in whom MRI-visible lesions were monitored by MRI-TRUS fusion biopsy.[19] The study categorized patients into 2 groups: National Institutes of Health low-risk (defined as International Society of Urological Pathology grade group 1) and National Institutes of Health intermediate-risk (International Society of Urological Pathology grade group 2) (see Table 10). Pathologic disease progression was defined as any International Society of Urological Pathology grade group 2 and 3 identified on surveillance biopsy in National Institutes of Health low- and intermediate-risk groups, respectively. During a mean follow-up of 25.5 months, 49 (29.5%) patients had pathologic disease progression. MRI-TRUS targeted biopsy alone identified 22 (45%) of 49 patients who progressed compared with TRUS biopsy alone, which identified 15 (31%) of 49 patients (p=0.03) (see Table 11). The number needed to biopsy to detect 1 pathologic progression was 7.96 (215/27) for TRUS biopsy and 3.14 (107/34) for MRI-targeted biopsy (p<0.001).

Ma et al (2017) reported on a single-center retrospective cohort study of 103 men with prostate cancer who were in active surveillance and underwent both TRUS-guided prostate biopsy and MRI-TRUS fusion.[20] They compared the detection rates for higher grade (Gleason score ≥7) prostate cancer for these techniques (see Table 10). Of the 25 (24.3%) men in the cohort that 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 11). 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.

Da Rosa et al (2015) conducted a prospective cohort study of 72 men with prostate cancer in active surveillance from 2011 to 2012 (see Table 10).[21] The study reported that MRI-TRUS fusion prostate biopsy showed a trend toward detecting more clinically significant cancers in active surveillance patients with substantially fewer cores than a systematic biopsy (see Table 11). 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 who had a systematic biopsy. To avoid bias, the operator who performed systematic biopsy following the MRI-TRUS fusion biopsy was blinded to the location of suspicious lesions on MRI.

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 10).[22] The study reported higher detection rates for disease progression by MRI-TRUS fusion biopsy than by systematic biopsy (see Table 11). 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 10. Summary of Key Observational Study Characteristics for MRI-Targeted and MRI-TRUS Fusion Biopsy

Study	Type	Location	Dates	MRI-Targeted Biopsy	MRI-TRUS Fusion Biopsy	Median FU, mo
Frye et al (2017)[19,a]	Paired retrospective cohort	U.S.	2007-2015	166	166	25.5
Ma et al (2017)[20]	Paired retrospective cohort	U.S.	2014-2015	103	103	60
Da Rosa et al (2015)[21]	Prospective cohort	Canada	2011-2012	72	72	38
Walton Diaz et al (2015)[22]	Paired retrospective cohort		2007-2014	58	58	16.1

FU: follow-up; MRI: magnetic resonance imaging; TRUS: transrectal ultrasound.
[a] Study population includes only men with lesions identified on multiparametric magnetic resonance imaging.

Table 11. Summary of Key Observational Studies for MRI-Targeted Biopsy, MRI-TRUS Fusion Biopsy, and Both Methods

Study	Diagnostic Yield With GS Upgrading, % (n/N)			GS ≥7 Cancer Detection, % (n/N)		
	Comparators	Outcome Rate	p	Comparators	Outcome Rate	p
Frye et al (2017)[19]	MRI-TRUS fusion only	44.9 (22/49)[a,b]				
	Systematic TRUS only	30.6 (15/49)[a,b]	0.03			
	Both	24.5 (12/49)[a,b]				
Ma et al (2017)[20]				MRI-TRUS fusion	6.8 (7/103)	0.002
				Systematic	20.4 (21/103)	
Da Rosa et al (2015)[21]	MRI-TRUS fusion	87 (13/15)		MRI-TRUS fusion	37 (7/19)[b]	0.18
	Systematic	67 (10/15)		Systematic	11 (2/19)[b]	
				Both	53 (10/19)[b]	
Walton Diaz et al (2015)[22]	MRI-TRUS fusion	53 (9/17)				
	Systematic	35 (6/17)				
	Both	12 (2/17)				

GS: Gleason score; HR: hazard ratio; MRI: magnetic resonance imaging; TRUS: transrectal ultrasound.
[a] Study population includes only men with lesions identified on multiparametric MRI.
[b] Reference is pathologic progression/GS ≥7 cases detected by either methods or by 2 methods combined.

Section Summary: Clinically Valid
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 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 (i.e., 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 would be expected to be similar among men on active surveillance.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Currently, there is no direct evidence from studies demonstrating that MRI-targeted prostate biopsies result in improved patient outcomes (e.g., survival, quality of life) among prostate cancer patients who are in active surveillance.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

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 parameter used in recommending definitive therapy in this population.

Gordetsky et al (2018) retrospectively compared management decisions in patients who had prostate cancer and received TRUS-guided biopsy with or without fusion MRI-targeted biopsy.[23] There were a number of significant baseline differences between the standard cohort (n=215 patients) who received TRUS biopsy alone and the target cohort (n=133 patients) who received an additional targeted biopsy of suspicious areas identified by MRI-TRUS fusion. Most patients had the disease of grade 1 or 2. A significantly higher proportion of patients in the target cohort elected active surveillance (49.6%) than in the standard cohort (24.2%; p<0.001). When given a choice between radiotherapy and prostatectomy, fewer patients in the target cohort (24.4%) chose the former, compared with the standard cohort (47.2%; p<0.001). Those who underwent MRI-guided biopsy were more likely to have had a previous positive biopsy (multivariate analysis, p=0.013), but no between-group difference was observed in PSA level prior to the biopsy (p=0.11). Multivariate analysis indicated that race was a predictive factor in disease management, with fewer African American men electing active surveillance than non-African American patients (p=0.013). Limitations included baseline differences between cohorts and a lack of analysis of socioeconomic status as a predictive factor in management choices. Overall, active surveillance was more likely to be chosen by patients who had MRI-targeted biopsy than by men who received TRUS biopsy alone.

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 2 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 the discussion of the clinical utility of MRI-targeted biopsy among biopsy-naive or previously biopsy-negative populations, there is evidence favoring 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. Eventually, this would improve survival, reduce morbidity, and improve the quality of life.

Summary: Disease Progression during Active Surveillance
For individuals who have prostate cancer, are in active surveillance, and have received an 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, an 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 (e.g., survival, quality of life) in this population.

Summary of Evidence
For individuals who have a suspicion of prostate cancer who receive an MRI-targeted biopsy, the evidence includes numerous prospective and retrospective studies of paired cohorts, 2 RCTs and systematic reviews and meta-analyses of these studies comparing MRI-targeted biopsy with TRUS-guided biopsy in detecting overall, clinically significant and 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 an 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, an 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 (e.g., survival, 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 (v.2.2018) on prostate cancer early detection make the following statement on the use of multiparametric magnetic resonance imaging (MRI) in the staging of prostate cancer[25]:

> "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 the use of MRI plus 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 (2016) has issued appropriateness criteria that stated[26]:

> "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.[27] 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 and Society of Abdominal Radiology (2016) published joint guidelines on prostate MRI and MRI-targeted biopsy for patients with prior negative biopsy. The groups recommended[28]:

> "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."

American Urological Association

The American Urological Association (2017) published a position statement on multiparametric MRI for diagnosis, staging, and management of prostate cancer.[29] While noting that multiparametric MRI is used increasingly to guide initial biopsy in biopsy-naive men, to confirm presumed localized prostate cancer, and to select a definitive therapy, the Association concluded that the evidence was insufficient to recommend MRI for screening, staging, or surveillance of prostate cancer. Indications for population-based screening using MRI were deemed investigational, and the Association recommended that individual patients review risks and benefits with their caregivers to make a shared decision.

U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force recommendations for MRI-targeted or MRI-TRUS 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 12.

Table 12. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01883128	An Evaluation of a Novel Imaging Based Complex Diagnostic and Therapeutic Pathway Intervention for Men Who Fail Radiotherapy for Prostate Cancer	177	Oct 2019
NCT02242773	MRI-Guided Biopsy Selection of Prostate Cancer Patients for Active Surveillance Versus Treatment: The Miami MAST Trial	165	Oct 2020
Unpublished			
NCT02138760	Comparison of MRI Fusion Biopsy Techniques in Men With Elevated PSA and Prior Negative Prostate Biopsy	400	Dec 2015 (unknown)
NCT00775866	MRI - Guided Biopsy for Suspicion of Locally Recurrent Prostate Cancer After External Beam Radiotherapy	82	Sep 2017 (completed)
NCT02564549	MRI-Based Active Surveillance to Avoid the Risks of Serial Biopsies in Men With Low-Risk Prostate Ca	28	Oct 2017 (terminated)
NCT02380027	PRostate Evaluation for Clinically Important Disease: Sampling Using Image-guidance Or Not? (PRECISION)	500	Dec 2017 (completed)

NCT: national clinical trial.

Appendix

Appendix Table 1. Comparison of Articles Included in Systematic Reviews

Studies Selected	Wegelin et al (2017)[4]	Wu et al (2015)[5]	Schoots et al (2015)[6]
Baco et al (2015)		●	
Belas et al (2012)			●
Boesen et al (2014)	●		
Borkowetz et al (2015)		●	
Costa et al (2013)			●
de Gorski et al (2015)		●	
Delongchamps et al (2013)	●	●	
Durmus et al (2013)			●
Fiard et al (2013)	●	●	●
Haffner et al (2011)			●
Iwamoto et al (2003)	●		
Jambor et al (2014)	●		
Junker et al (2015)		●	
Kauffman et al (2014)	●		
Kuru et al (2013)	●	●	
Miyagawa et al (2010)	●	●	
Mouraviev et al (2013)			
Mozer et al (2014)	●	●	●
Park et al (2008)			●
Park et al (2011)	●		●
Pepe et al (2015)	●		
Pokorny et al (2014)	●		●
Portalez et al (2012)	●		●
Puech et al (2013)	●	●	●

Studies Selected	Wegelin et al (2017)[4]	Wu et al (2015)[5]	Schoots et al (2015)[6]
Quentin et al (2014)	●		
Rastinehad et al (2014)	●	●	●
Rud et al (2012)			●
Salami et al (2014)	●		
Salami et al (2015)	●		
Shakir et al (2014)	●		
Shoji et al (2014)	●		
Siddiqui et al (2013)			●
Siddiqui et al (2015)		●	
Sonn et al (2013)	●	●	●
Sonn et al (2014)			
Ukimura et al (2015)		●	
Vourganti et al (2012)	●	●	
Wysock et al (2013)	●	●	●

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Documentation for Clinical Review

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
  - Clinical findings (i.e., pertinent symptoms and duration)
  - Reason for magnetic resonance imaging (MRI)-Targeted Biopsy
  - Past and present diagnostic testing and results (i.e., initial biopsy and digital rectal exam)
- Prostate-specific Antigen (PSA) Test results

Post Service

- Results/reports of tests performed
- Procedure report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

MN/NMN
The following services may be considered medically necessary when policy criteria are met. Services may be considered not medically necessary when policy criteria are not met.

Type	Code	Description
CPT®	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
	77021	Magnetic resonance guidance for needle placement (e.g., for biopsy, needle aspiration, injection, or placement of localization device) radiological supervision and interpretation
HCPCS	None	
ICD-10 Procedure	0VB03ZX	Excision of Prostate, Percutaneous Approach, Diagnostic
	0VB04ZX	Excision of Prostate, Percutaneous Endoscopic Approach, Diagnostic
	0VB07ZX	Excision of Prostate, Via Natural or Artificial Opening, Diagnostic
	0VB08ZX	Excision of Prostate, Via Natural or Artificial Opening Endoscopic, Diagnostic

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
07/01/2016	BCBSA Medical Policy Adoption	Medical Policy Committee

Effective Date	Action	Reason
10/01/2017	Policy revision with position change	Medical Policy Committee
10/01/2018	Policy revision without position change	Medical Policy Committee

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.