Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

***Current Policy Effective Date: 5/1/25**
(See policy history boxes for previous effective dates)

Title: Magnetic Resonance Imaging – Targeted Biopsy of the Prostate

Description/Background

Before a transrectal ultrasound (TRUS)-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.

Magnetic resonance imaging and transrectal ultrasound (MRI-TRUS) fusion-guided biopsy uses software to combine detailed images obtained from an MRI with the less detailed real-time TRUS, through an overlaid 3-dimensional view. These “fused” images guide the placement of the biopsy needle to suspicious lesions identified from the MRI for prostate biopsy.

Prostate Cancer

Prostate cancer is the most common cancer diagnosed in men and the second leading cause of cancer death among men in the U.S. According to the National Cancer Institute, there were an estimated 288,300 new cases and 34,700 deaths in 2023.(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 definitive intervention (higher-grade tumors). Patients in active surveillance undergo periodic follow-up prostate biopsies to assess cancer progression (upgrading of Gleason score).

Prostate biopsies are commonly 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 over diagnose clinically insignificant disease and under diagnose 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 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, under sampling (or not sampling nontarget areas),and sampling of clinically significant disease (higher grade tumor). T2-weighted images reflect the 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 non-specificity 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, a 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 the 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.

The technique of MRI-TRUS fusion biopsy, done visually or using software, superimposes pre-procedure (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
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. There is also evidence evaluating whether the MRI-targeted biopsy should replace the systematic 12-coreTRUS biopsy.

Proposed clinical indications for use of MRI-targeted prostate biopsy include: (1) as initial biopsy, (2) re-biopsy 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) to determine initial eligibility for active surveillance or follow-up for active surveillance in assessing disease progression over time, and (4) for local recurrence 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). A 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).

Medical Policy Statement

The safety and effectiveness of a prostate biopsy using an FDA approved magnetic resonance imaging guided device, including the direct (in-bore) approach, and fusion imaging of multi-parametric MRI with TRUS has been established. It may be considered useful when criteria are met.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Inclusions:
The use of magnetic resonance imaging (MRI), both direct (in-bore) or MRI-TRUS fusion, to guide targeted biopsy of the prostate for cancer when **one** of the following criteria are met:

- As **initial/repeat biopsy** when there is a suspicion for prostate cancer (i.e., rising/elevated prostate specific antigen [PSA][a] or very suspicious digital rectal exam [DRE])

- To guide **management** when life expectancy is greater than 10 years and **one** of the following are met:
  - Active surveillance for very-low, low, or favorable intermediate-risk of prostate cancer
  - Re-biopsy 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
  - To determine initial eligibility for active surveillance
  - To assess progression of disease over time
  - For local recurrence after external-beam radiotherapy, or after high-intensity focused ultrasound.

*[a] Elevated PSA levels defined as > 3 ng/ml in men 40-75 years old with high risk **or** 45-75 years old with average risk. PSA levels ≥ 4 ng/ml is considered elevated in men greater than 75 years old.*

***Note**: High risk individuals include: Black/African American individuals, those with germline mutations that increase the risk for prostate cancer, and those with concerning family or personal history.*

Exclusions:
The use of MRI in any of the following:
- To guide targeted biopsy of the prostate for any indications not listed above
- When used for individuals in observation

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

55700 55705 55706 77021

Other codes (investigational, not medically necessary, etc.):

N/A

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

Patients with a Suspicion of Prostate Cancer

Clinical Context and Test Purpose
The purpose of magnetic resonance imaging (MRI)-targeted prostate biopsy in men with suspicion of prostate cancer is to inform a decision whether the patient has prostate cancer that requires definitive treatment or active surveillance for prostate cancer.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest are men with suspicion of prostate cancer. Suspicion includes elevated prostate specific antigen (PSA) levels and/or clinical symptoms of prostate cancer.

Interventions
The relevant interventions of interest are MRI-targeted biopsy, including the following 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: standard TRUS-guided 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., overall survival, disease-specific survival, morbid events, and quality of life).

Specific outcomes include (1) improving the detection of clinically significant prostate cancer; (2) increasing accurate risk stratification; and (3) 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.

Table 2. Outcomes of Interest for Individuals with Suspicion of Prostate Cancer

Outcomes	Details
Test accuracy	Outcomes of interest include overall prostate cancer detection, clinically significant prostate cancer detection, sensitivity, and specificity. [Timing: ≥1 week]

Study Selection Criteria
For the evaluation of clinical validity of MRI-targeted biopsy of the prostate, studies that meet the following eligibility criteria were considered:
- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

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).

Review of Evidence

Systematic Reviews
Several systematic reviews have been published that have compared the diagnostic performance of MRI-targeted biopsy, TRUS-guided biopsy, and/or their combination in detecting prostate cancer.(3-12) Despite variation in scope in terms of study designs and populations, definition of clinically significant prostate cancer, and analysis methods, these reviews have generally consistently reported significantly improvements with the MRI-targeted biopsy techniques in detecting clinically significant prostate cancer compared with TRUS-guided biopsy. A sampling of several of the most recent reviews are discussed below.

The largest systematic review is a Cochrane review reported by Drost et al (2020),(9) which compared the diagnostic accuracy of MRI only, MRI-targeted biopsy, MRI pathway (MRI with or without MRI-targeted biopsy), and systematic biopsy in detecting clinically significant prostate cancer as compared with a reference standard of template-guided biopsy. Based on a

search of several electronic databases through July 2018, this review included 43 studies of a total of 6,871men. Of the 43 studies, 18 conducted diagnostic test accuracy analyses and 25 were agreement analyses. The majority of study participants were biopsy-naïve (77%, n=5,353). Clinically significant prostate cancer was defined as International Society of Urological Pathology grade II or higher. In the diagnostic test accuracy studies, the sensitivity rates to detect clinically significant prostate cancer using MRI-targeted biopsy, MRI pathway, and systematic biopsy were 80%, 72%, and63%, respectively (see Table 3). Specificity rates using MRI-targeted biopsy, MRI pathway, and systematic biopsy were 94%, 96%, and 100%, respectively. In the studies that reported agreement analyses, pooled detection ratios were significantly greater overall for the MRI pathway compared with systematic biopsy (1.12; 95% CI, 1.02-1.23). However, the improved detection ratio for the MRI pathway was primarily driven by findings in studies of men with prior negative biopsies (detection ratio 1.44; 95% CI, 1.19-1.75). The improvement with the MRI pathway in the biopsy-naïve studies did not reach statistical significance (detection ratio 1.05; 95% CI, 0.95-1.16). The authors noted that the certainty in their findings was generally low, however, as a considerable number of studies had a high or unclear risk of bias.

Table 3. Results of Different Biopsy Approaches in Detecting Clinically Significant Prostate Cancer[a]

Variables	MRI pathway (MRI with or without MRI-targeted biopsy)	MRI-targeted biopsy	Systematic biopsy
Sensitivity (95% CI)	0.72 (0.60 to 0.82)	0.80 (0.69-0.87)	0.63 (0.19-0.93)
Specificity (95% CI)	0.96 (0.94 to 0.98)	0.94 (0.90-0.97)	1.00 (0.91-1.00)
Results per 1000 men tested (95% CI): at a baseline prevalence of 30% ISUP grade ≥ 2 prostate cancer by the reference test			
True positives:	216 (180-246)	240 (207-261)	189 (57-279)
False negatives:	84 (54-120)	60 (39-93)	111 (21-243)
True negatives:	672 (658-686)	658 (630-679)	700 (637-700)
False positives	28 (14-42)	42 (21-70)	0 (0-63)

Adapted from Drost et al (2020).
[a]International Society of Urological Pathology grade ≥ 2 prostate cancer
CI: confidence interval; MRI: magnetic resonance imaging; ISUP: International Society of Urological Pathology

Results also consistently demonstrated improved detection of clinically significant prostate cancer for MRI-targeted biopsy techniques in two concurrently conducted systematic reviews that focused only on biopsy-naïve men. Elwenspoek et al (2019),(8) conducted a systematic review (literature search through December 2018) of seven randomized controlled trials[RCTs] published from 2011 to 2018 (total N=2582, n range, 103-1140) that evaluated the diagnostic performance of two MRI pathways (MRI plus targeted and systematic biopsy and MRI plus targeted biopsy alone) compared to systematic biopsy alone. These RCTs are summarized below. All RCTs were conducted outside of the United States. The review evaluated the rate of patients diagnosed with clinically significant or insignificant prostate cancer as defined by the individual studies. Definitions of clinically significant prostate cancer varied across studies, but all involved a Gleason score of 6 or greater. Some examples include “Gleason score ≥6 and histologically confirmed with adenocarcinoma", “presence of a single biopsy core indicating disease of GS ≥7”, “any Gleason score ≥7 or CCL ≥5 mm” and more. Risk of bias was assessed using the revised Cochrane tool and the majority of RCTs were judged to have a low overall risk of bias. Compared with systematic biopsy alone, MRI with or without targeted biopsy was associated with significant improvement in the detection of clinically significant prostate cancer (+57%; 95% CI, 2%-141%). However, compared with systematic biopsy alone, the MRI plus targeted and systematic biopsy pathway did not significantly improve the rate of clinically significant prostate cancer detection (risk ratio, 1.36; 95% CI, 0.79-2.34. Additionally, comparison between the two prebiopsy MRI pathways showed mixed results. Results were similar in another systematic review by Tu et al (2020),(12) that included 6 RCTs and 25 own-

control cohorts. Searches for the review by Tu et al (2020) were also through December 2018 and the addition of the own-control cohort studies resulted in a total of 4,020 biopsy-naïve men. Although the thresholds for clinically significant prostate cancer (Gleason score of 3 or 4) were generally lower than in the systematic review by Elwenspoek et al (2019), this review by Tu et al also found a significant increase in detection rate for MRI-targeted biopsy compared with systematic biopsy (risk ratio, 1.20; 95% CI, 1.07-1.34).

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.(4) 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 (three cohorts; n=528 patients), or (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). Inpatients 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 two 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.(5) Twenty-five studies compared detection rates of all 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 a higher sensitivity to detect clinically significant prostate cancer than TRUS-guided biopsy (sensitivity, 79%). MRI-targeted biopsy (sensitivity, 7%) had a 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.(6) In 16 trials (1 RCT, 15 paired cohort studies), a total of 3105 participants underwent MRI-TRUS fusion or TRUS-guided biopsy. 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 an overall prostate cancer diagnosis than TRUS-guided biopsy, with moderate heterogeneity between trials (see Tables 4 and 5). Among 10 trials that compared the detection rate of clinically significant prostate

cancer between these two 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).

Table 4. Systematic Review Results (Relative Risk, Relative Sensitivity) of Prostate Cancer Detection for MRI-Targeted and TRUS-Guided Biopsies

Study	Trials	Sample Size[a]	Outcome: Detection Rates	RR/RS	95% CI	p	I^2, %
Wegelin et al (2017)	25	3520	Prostate cancer	0.98	0.90 to 1.07	NR	NR
	14	2328	Clinically significant prostate cancer	1.16	1.02 to 1.32	NR	NR
	14	2328	Clinically insignificant prostate cancer	0.47	0.35 to 0.63	NR	NR
Wu et al (2015)	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

[a]For Wu et al (2015), sample size is displayed as MRI/ultrasound fusion biopsy sample size/system biopsies sample size
CI: confidence interval; MRI: magnetic resonance imaging; NR: not reported; RR: relative risk; RS: relative sensitivity; TRUS: transrectal ultrasound.

Table 5. 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)	81 (76 to 85)	83 (77 to 88)	25	Relative sensitivity	0.98	0.90 to 1.07	NR	NR
	90 (85 to 94)	79 (68 to 87)	14	Relative sensitivity	1.16	1.02 to 1.32	NR	NR
	7 (4 to 10)	14 (11 to 18)	14	Relative sensitivity	0.47	0.35 to 0.63	NR	NR
Wu et al (2015)	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

CI: confidence interval; MRI: magnetic resonance imaging; NR: not reported; TRUS: transrectal ultrasound.

Randomized Controlled Trials

Many RCTs have been incorporated into systematic reviews and meta-analysis to date, with the exception of the following recent RCT. Klotz et al (2021) published a multicenter, phase 3, randomized, noninferiority trial of 453 biopsy-naïve men with suspicion of prostate cancer advised to undergo biopsy.(13) Patients were randomized to TRUS-guided biopsy (n=226; 225 evaluated) or MRI-targeted biopsy (n=227; 221 evaluated). A total of 83 (37%) patients in the MRI-targeted biopsy group had a negative MRI and did not receive a biopsy. A grade group 2 or greater prostate cancer was identified in 30% of patients in the TRUS-guided biopsy groups compared with 35% in the MRI-targeted biopsy group, which met the predefined threshold for noninferiority (absolute difference, 5%; 97.5% 1-sided CI, -3.4% to infinity; noninferiority

margin, -5%). Diagnosis of clinically insignificant cancers was lower in the MRI-targeted therapy arm compared with the TRUS-guided biopsy arm (10.1% vs 21.7%; absolute difference, 11.6%; 95% CI, -18.2% to -4.9%;p<.001). One limitation of this trial is the potential for undiagnosed cancer in patients that did not receive a biopsy. Patients with no diagnosis of prostate cancer or diagnosis of a grade group 1 tumor are being followed for 2 years, and follow-up data will be evaluated when all patients complete the 2-year follow up. All MRIs were interpreted by experienced radiologists, and generalizability to less experienced practitioners is limited. A 2-year follow-up of this trial was also conducted to evaluate patients who were diagnosed with clinically significant prostate cancer at baseline.(14) Two-year MRI scans were available for 69 patients in the TRUS-guided biopsy group and 75 patients in the MRI-targeted biopsy group. Of the evaluated patients, 51 (67%) in the TRUS-guided group and 55 (73%) in the MRI-targeted group had negative 2-year MRI results. Also at 2 years, 116/221 (52.5%) in the MRI-targeted biopsy group and 113/204 (55%) in the TRUS-guided biopsy group were free of grade group ≥2 disease, treatment, progression, or death from any cause (odds ratio [OR], 1.08; p =.66).

Eklund et al (2021) conducted a prospective, population-based, noninferiority trial involving 1532 men (50 to 74 years of age) with PSA levels ≥3 ng/mL who were randomly assigned in a 2:3 ratio to undergo a standard biopsy (n=603) or MRI with targeted and standard biopsy if the MRI results suggested prostate cancer (the experimental arm; n=929).(15) The primary outcome was the probability of detection of clinically significant prostate cancer, defined as the percentage of individuals in each group who received a cancer diagnosis with a Gleason score of 3+4 or greater. A key secondary outcome was the detection of clinically insignificant cancers (Gleason score 6). Of patients in the experimental arm, 338 (36%) underwent biopsies. In the standard biopsy group, 438 (73%) underwent biopsy. In the intention-to-treat analysis, clinically significant prostate cancer (Gleason score ≥7) was diagnosed in 192 (21%) patients in the experimental biopsy group versus 106 (18%) patients in the standard biopsy group, a 3% difference (95% CI, -1 to 7; p<.001 for noninferiority). The experimental biopsy group also experienced a lower percentage of clinically insignificant cancers than the standard biopsy group (4% vs. 12%; difference, -8%; [95% CI, -11 to -5]). This study was performed in Sweden, with centralized radiologic and pathological assessment, which may limit its generalizability to other settings. Additionally, the researchers completed only a single round of screening; therefore, whether the reduction in overdiagnosis will be retained through multiple screening rounds is unknown.

Wang et al (2023) published a multicenter RCT that compared TRUS-guided systematic biopsy (12 cores), MRI-guided biopsy (12 cores), and artificial intelligence ultrasound-guided biopsy (6 cores) in 400 patients with suspected prostate cancer.(16) The prostate cancer detection rate for the 3 biopsy strategies was 34.6%, 35.8%, and 49.6%, respectively (p=.036 for artificial intelligence-guided biopsy vs. TRUS-guided biopsy; p=.052 for artificial intelligence-guided biopsy vs. MRI-guided biopsy). Clinically significant prostate cancer detection rates were 26.3%, 23.1%, and 32.3%, respectively. The authors concluded that biopsy guided by artificial intelligence may become an alternative to systematic biopsy.

Observational Studies
Hugosson et al (2022) reported the results of a prospective cohort of 17,980 men aged 50 to 60 years with a screening PSA ≥3 ng/mL who underwent MRI followed by MRI-targeted biopsy and/or systematic biopsy.(17) The experimental group (n=11,986) received either systematic biopsy or MRI-guided biopsy. The reference group (n=5994) received both systemic and MRI-targeted biopsy. In the intent to treat analysis, clinically insignificant prostate cancer (Gleason score 3+3) was found in 1.2% of patients in the systematic biopsy group compared to 0.6% of patients in the MRI-targeted biopsy group (relative risk [RR], 0.46; 95% CI, 0.33 to 0.64; p<.001). Clinically significant prostate cancer (Gleason score 3+4) was found in 1.1% of the systematic biopsy group compared to 0.9% of the MRI-targeted biopsy group (RR, 0.81; 95% CI, 0.60 to 1.1). Ten patients had clinically significant cancer that was only detected by systematic biopsy. The authors concluded that overdiagnosis was reduced by half and few clinically significant cancers were missed with MRI-targeted biopsy among patients with elevated screening PSA levels.

Ahdoot et al (2020) reported on a prospective cohort study of 2103 men with MRI-visible prostate lesions who underwent both MRI-targeted and systematic biopsies at the National Cancer Institute between June 2007 through January 2019.(18) Prior to study enrollment, the majority of participants (79.3%) had undergone at least 1 previous biopsy. Cancer detection rates for all Gleason Grade groups were 52.5% (n=1104) for the systematic biopsy method, 51.5% (n=1084) for the MRI-targeted method, and 62.4% (n=1312) for the combined method. When detection rates were analyzed according to separate Grade groups, systematic biopsy alone was found to detect significantly more Grade I cancers than MRI-targeted biopsy alone (21.6% [n=454] versus 13.7% [n=289]; *P*<.001) and similar rates compared with the combined method (18.7%, n=394). For Grade II cancers, there were no significant differences between the systematic-alone method (17.1%; n=359), the MRI-targeted method alone (17.6%; n=370), and the combined method (21.5%; n=452). But, for Grades III-V, MRI-targeted biopsy led to the detection of significantly more cancers than systematic biopsy. Differences in cancer detection rates for the MRI-targeted method alone compared with the systematic method alone (95% confidence intervals; percentages of patients) were 1.7% (0.2% to 3.1%; 5.1% versus 3.5%) for Grade III, 3.7% (2.2% to 5.2%; 10.2% versus 6.5%) for Grade IV, and 1% (0.2% to 1.8%; 4.9% versus 3.9%) for Grade V. Compared with MRI- targeted biopsy alone, there were small additional gains with the combined method for Grades III, (5.9%, n=124),4 (10.8%, n=228) and 5 (5.4%, n=114), however, these were not statistically significant. The primary limitations of this study are related to relevance of its population (i.e., only MRI-visible lesions), setting (i.e., single-center) and delivery methods (i.e., use of a single experienced physician to perform the systematic biopsy and another to perform the MRI-directed biopsy).These factors have the potential to limit the generalizability of its findings to practice patterns in community institutions with less experienced practitioners and a broader range of patients.

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.(19) 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, 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, the 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 DRE result, or (2) confirmation of low-risk prostate cancer for patients considering active surveillance.(20) All patients underwent a mpMRI and regions of interest (ROIs) were graded as I to V. 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 one ROI of grade III or more, and 217 (21%) had no suspicious lesions noted on MRI (see Table 8). Among 825 patients with one or more ROI of grade III 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 9).

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).(21) 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 vs122 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 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. 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 8). 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 8).

Table 6. 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)	Prospective	U.S.	2009-2014	825	825
Siddiqui et al (2015)	Prospective	U.S.	2007-2014	1003	1003

MRI: magnetic resonance imaging; TRUS: transrectal ultrasound.

Table 7. 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)	MRI-TRUS fusion only	28 (229/825)[b]	<0.001	MRI-TRUS fusion	44 (360/825)
	Artemis-guided systematic only	24 (199/825)[b]		Systematic	49 (307/825)
	Combined	35 (289/825)[b]		Combined	60 (493/825)
Siddiqui et al (2015)	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; 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 8. 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).[16]
AUC: area under the curve; CI: confidence interval; MRI: magnetic resonance imaging; TRUS: transrectal ultrasound.

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.(22) 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 five-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.(23) Among the 450 patients with a mean follow-up of eight 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.(24) 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: Patients with a Suspicion 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, 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 a clinically meaningful improvement in outcomes (e.g., survival or quality of life).

Patients with Prostate Cancer and in Active Surveillance

Clinical Context and Test Purpose

The purpose of MRI-targeted prostate biopsy in individuals with prostate cancer and in active surveillance is to detect disease progression.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest are men with prostate cancer and in active surveillance.

Interventions

The relevant intervention of interest is MRI-targeted biopsy, which includes the following 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 underactive surveillance: standard 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 (i.e., overall survival, disease-specific survival, morbid events, and quality of life) (Table 9).

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.

Table 9. Outcomes of Interest for Individuals with Prostate Cancer and in Active Surveillance

Outcomes	Details
Test accuracy	Outcomes of interest include overall prostate cancer detection, clinically significant prostate cancer detection, sensitivity, and specificity. [Timing: ≥1 week]

Study Selection Criteria

For the evaluation of clinical validity of MRI-targeted biopsy of the prostate, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

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).

Review of Evidence

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.(25) 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 two main clinical questions: (1) Can MRI-targeted biopsy detect clinically significant disease in men in 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 three distinct populations of men-group I: men with histologic suitability for active surveillance who chose radical prostatectomy and had an MRI performed preoperatively (n=10 studies); group II: men in active surveillance who had an MRI before a confirmatory biopsy (n=7 studies); and group III: 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 I), repeat standard biopsy (groups II and III), or biopsies targeted to any suspicious lesions on MRI (groups II and III). 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 six. 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 preoperative MRI. 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 MRIs.

Seven studies assessed repeat biopsy data for men on active surveillance who had a prior MRI (group II). Four studies performed MRI-targeted biopsies plus TRUS-guided biopsies, and three studies only performed repeat standard (TRUS) biopsy following MRI. MRI-targeted biopsies were performed using software-registered MRI-TRUS fusion in two of the four studies, visual registered (cognitive) MRI-TRUS fusion in one study, and direct in-bore in one 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

One randomized controlled trial was identified that compared MRI-targeted biopsy with TRUS-guided biopsy in men on active surveillance for prostate cancer. Klotz et al (2019, 2020),(26,27) reported on the ASIST trial (Active Surveillance Magnetic Resonance Imaging Study), a randomized, multicenter, open-label trial in Canada that evaluated 273 men recently

diagnosed with grade group I prostate cancer (see Table 10). The primary end point of ASIST was the proportion of patients upgraded to prostate cancer Grade Group II or greater and the power calculation was based on a 1-sided Fisher's exact test and required 266 total patients. The initial results at the time of the confirmatory biopsy did not show a significant benefit for MRI-targeted biopsy (Table 11). However at the 2-year biopsy, use of MRI led to significantly less disease progression than no MRI. However, interpretation of findings from this study may be limited by the presence of the design, conduct, and relevance limitations described in Table 10.

Schiavina et al (2021) conducted an RCT in Italy that evaluated 124 men diagnosed with prostate cancer after random biopsy (Table 10).(28) The primary endpoint of the trial was the reclassification rate at 12 month random biopsy in the experimental versus control groups. Reclassification was defined as a biopsy International Society of Urological Pathology (ISUP)-grade group grade 1 in >2 biopsy cores or biopsy ISUP-grade group grade ≥2. Major results are presented in Table 11. The early use of multiparametric MRI for active surveillance in men with low-risk prostate cancer after random biopsy significantly reduces reclassifications at a 12 month random biopsy. Design, conduct, and relevance limitations of this trial are stated in Table 10.

Table 10. Summary of Key RCT Characteristics for Active Surveillance

Study; Trial	Countries	Sites	Dates	Participants	Study Groups		Design and conduct limitations	Relevance limitations
					Group 1	**Group 2**		
Klotz et al (2019, 2020); ASIST	Canada	3	2011-2015	Men diagnosed with Grade 1 prostate cancer within the past year being managed with active surveillance	12-core systematic biopsy, n=136	MRI with systematic and targeted biopsy using the Artemis fusion targeting system, n=137	• Possible inadequate control for selection bias: Patients in MRI group had less cancer overall (15% vs. 23%)	• Intervention delivery method relevance limitations: Scoring performed in time period predating 2016 release of PI-RADS v2; inexperience with fusion targeted biopsies may have underestimated benefits of MRI
Schiavina et al (2021)	Italy	3	2015-2018	Men between 35 and 75 years of age diagnosed with prostate cancer after random biopsy fulfilling PRIAS criteria	Manage-ment according to PRIAS schedule and 12-core random biopsy at 12 months, n=62	Multipara-metric MRI at 3 months and fusion-targeted biopsy with positive findings, n=62	• Due to the study design, the timeline of reclassificatio n was asymmetrical, as the control group was reclassified only at 12 months • Enrolled population relatively small	• Study designed in 2015 when random biopsy was the gold standard in naive patients and the evidence regarding the role of multiparamet ric MRI was not as robust as the

	current time period

RCT: randomized controlled trial; ASIST: Active Surveillance Magnetic Resonance Imaging Study; MRI: magnetic resonance imaging; PI-RADS: Prostate Imaging Reporting And Data System

Table 11. Key Results of RCTs of MRI-Targeted Versus Systematic Biopsies in Active Surveillance

Study	Detection of Disease Progression	Progression-free (PF) survival
Klotz et al (2019, 2020); ASIST	• At time of confirmatory biopsy[a]: 33% (42/127) vs 27% (36/132); *P*=.3 • 2-yr repeat biopsy[a]: 9.9% (8/81) vs 23% (17/75); *P*=.048	• 1-yr PF estimate (95% CI): 75% (67%-82%) versus 73.4% (64.9%-80.1%) • 2-yr PF survival: 88% vs 77%; *P*=.009
	Reclassification rate at 12 month random biopsy	Rate of adverse pathological features at 12 months
Schiavina et al (2021	• 6.5% vs. 29%; p<.001	• 0% vs. 55.6%; p=.04

ASIST: Active Surveillance Magnetic Resonance Imaging Study; CI: confidence interval; MRI: magnetic resonance imaging; RCT: randomized controlled trial.
[a]Gleason Grade upgraded to 2 or greater
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.(29) The study categorized patients into 2 groups: National Institutes of Health low-risk (defined as International Society of Urological Pathology [ISUP] grade group I) and National Institutes of Health intermediate-risk (International Society of Urological Pathology grade group II) (see Table 12). Pathologic disease progression was defined as any International Society of Urological Pathology grade group II and III 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 13). The number needed to biopsy to detect one 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 12). 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, four by MRI-TRUS fusion biopsy, and three by both (see Table 13). MRI-TRUS fusion biopsy alone had a lower sensitivity to detect cancer with a Gleason score of seven 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 12).(31) 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

13). Additionally, MRI-TRUS fusion biopsy identified three Gleason score upgrades that would not have been detected with systematic biopsy alone and upgraded a Gleason score by two or more in five patients compared with one 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 12).(32) The study reported higher detection rates for disease progression by MRI-TRUS fusion biopsy than by systematic biopsy (see Table 13). 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 12. 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)	Paired retrospective cohort	U.S.	2007-2015	166	166	25.5
Ma et al (2017)	Paired retrospective cohort	U.S.	2014-2015	103	103	60
Da Rosa et al (2015)	Prospective cohort	Canada	2011-2012	72	72	38
Walton Diaz et al (2015)	Paired retrospective cohort		2007-2014	58	58	16.1

FU: follow-up; MRI: magnetic resonance imaging; NR: not reported; TRUS: transrectal ultrasound.
[a] Study population includes only men with lesions identified on multiparametric magnetic resonance imaging.

Table 13. 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)	MRI-TRUS fusion only	44.9 (22/49)[a,b]	0.03	NR	NR	NR
	Systematic TRUS only	30.6 (15/49)[a,b]		NR	NR	
	Both	24.5 (12/49)[a,b]		NR	NR	
Ma et al (2017)				MRI-TRUS fusion	6.8 (7/103)	0.002
				Systematic	20.4 (21/103)	
Da Rosa et al (2015)	MRI-TRUS fusion	87 (13/15)	NR	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)	MRI-TRUS fusion	53 (9/17)	NR	NR	NR	NR
	Systematic	35 (6/17)		NR	NR	
	Both	12 (2/17)		NR	NR	

[a] Study population includes only men with lesions identified on multiparametric MRI.
[b] Reference is pathologic progression/GS ≥7 cases detected by either method or by 2 methods combined.
GS: Gleason score; MRI: magnetic resonance imaging; NR: not reported; TRUS: transrectal ultrasound.

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 seven 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.(33) 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 I or II. 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 the 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.(34) 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 a 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-naïve 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.

Section Summary: Patients with Prostate Cancer and in Active Surveillance
The evidence for the use of MRI-targeted surveillance prostate biopsy includes an RCT, 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 in active surveillance

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, RCTs and systematic reviews and meta-analyses of these studies. Available studies compared 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 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 an 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, an RCT, 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 an improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this policy are listed in Table 14.

Table 14. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02242773	MRI-Guided Biopsy Selection of Prostate Cancer Patients for Active Surveillance Versus Treatment: The Miami MAST Trial	165	Jul 2024
NCT04081636	Prostate Biopsy: Reducing Complications and Improving Efficacy (ProBE-PC Randomized Trial)	830	Mar 2024

NCT: national clinical trial.

Supplemental Information

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

National Comprehensive Cancer Network (v.4.2024) on prostate cancer makes the following statements on the use of multiparametric magnetic resonance imaging (MRI) in the staging of prostate cancer:(35)

“Multiparametric MRI (mpMRI) can be used in the staging and characterization of prostate cancer.”

“mpMRI may be used to better risk stratify patients who are considering active surveillance. Additionally, mpMRI may detect large and poorly differentiated prostate cancer (Grade Group ≥2) and detect extracapsular extension (T staging) and is preferred over CT for abdominal/pelvic staging. mpMRI has been shown to be equivalent to CT scan for pelvic lymph node evaluation.”

National Comprehensive Cancer Network (v.2.2024) on prostate cancer early detection recommends the following in their guidelines on the use of multiparametric magnetic resonance imaging (MRI) for the early detection of prostate cancer:(41)
Mulitparametric MRI (mpMRI is considered a category 1, if available, when a further evaluation and/or biopsy is indicated (the level of PSA correlates with the risk of prostate cancer). During management of prostate cancer, guidelines state that in patients undergoing biopsy, targeting using MRI/ultrasound fusion significantly increases the detection of clinically significant, higher-risk (Grade Group ≥3) disease while lowering the detection of lower-risk (Grade Group 1 or lower-volume Grade Group 2) disease. It is strongly recommended that image-guided biopsy techniques be employed routinely. Radiologic expertise and the use of high-quality mpMRI hardware is essential for optimal interpretation of scans. Most advocate for a combined targeted and systematic biopsy approach as some high-grade cancers are uniquely detected using the systematic approach and systematic biopsies are needed for risk stratification if cancer is found. However, some advocate for excluding systematic biopsy in those undergoing MRI targeting due to concerns that it may increase the risk of overdiagnosis

American College of Radiology
In 2022, the American College of Radiology has issued appropriateness criteria that stated:(36)

- "the clinical paradigm for prostate cancer diagnosis undoubtedly is rapidly moving toward MRI-targeted biopsies, based on abundant evidence that this can improve pretreatment evaluation of prostate cancer in many aspects, such as MRI-targeted biopsies are more concordant with radical prostatectomy in determining Gleason score; better selected candidates for active surveillance; and improved risk stratification"
- "clinical pathways that incorporate MRI-targeted biopsy have been shown to increase the detection rate of clinically significant cancers, especially in patients who had a prior negative [transrectal ultrasound]-guided biopsy with continuous suspicion for prostate cancer and even in biopsy-naïve patients"
- "MRI-targeted biopsy may be useful in a subset of patients with Gleason 3 + 4 for the purpose of identifying “favorable intermediate-risk” who may be considered for active surveillance"
- "MRI-targeted biopsies have shown increasing usage for active surveillance during the past decade for reclassification of disease as part of determining eligibility or during follow up....because some tumors are invisible on MRI and missed by MRI-targeted biopsies, even when performing an MRI-targeted biopsy as part of active surveillance, concurrent systemic biopsies cannot be omitted at the moment."

In 2022, the American College of Radiology issued appropriateness criteria for post-treatment follow-up of prostate cancer, noting that MRI-targeted biopsy may be appropriate for follow-up status post radical prostatectomy when there is clinical concern for residual disease.(37) For follow-up in patients with clinical concern for residual or recurrent disease following nonsurgical local and pelvic treatments, MRI-targeted biopsy is usually appropriate.

National Institute for Health and Care Excellence
In 2019, the National for Health and Care Excellence published guidelines on the diagnosis and management of prostate cancer with the following recommendations:(38)

- "Do not routinely offer multiparametric MRI to people with prostate cancer who are not going to be able to have radical treatment."
- "Offer multiparametric MRI as the first-line investigation for people with suspected clinically localised prostate cancer. Report the results using a 5-point Likert scale."
- “Offer multiparametric MRI-influenced prostate biopsy to people whose Likert score is 3 or more.”
- “Consider omitting a prostate biopsy for people whose multiparametric MRI Likert score is 1 or 2, but only after discussing the risks and benefits with the person and reaching a shared decision. If a person opts to have a biopsy, offer systematic prostate biopsy.”

American Urological Association and Society of Abdominal Radiology
In 2016, the American Urological Association and Society of Abdominal Radiology published a joint consensus statement on prostate MRI and MRI-targeted biopsy for patients with prior negative biopsy. The groups recommended:(39)

"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
In 2020, the American Urological Association published an update of the standard operating procedure on the use of multiparametric MIRI for the diagnosis, staging, and management of prostate cancer.(40) The statement concluded that "data support prostate MRI use in men with a previous negative biopsy and ongoing concerns about increased risk of prostate cancer. Sufficient data now exist to support the recommendation of MRI before prostate biopsy in all men who have no history of biopsy. Currently, the evidence is insufficient to recommend MRI for screening, staging, or surveillance of prostate cancer."

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.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this policy are listed in Table 14 .

Table 14. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02242773	MRI-Guided Active Selection for Treatment of Prostate Cancer : The Miami MAST Trial	207	Sep 2024
NCT04081636	Prospective, Randomized Study Comparing Transperineal and Transrectal Prostate Biopsy Efficacy and Complications (ProBE-PC Trial)	840	Dec 2025
NCT04692675	Multiparametric Magnetic Resonance Imaging of the Prostate to Assess Disease Progression and Genomics in Patients Undergoing Active Surveillance for Prostate Cancer	508	Sep 2027

NCT: national clinical trial.

Government Regulations

National:

National Coverage Determination: Prostate Cancer Screening Tests. Pub 100-3, Manual Section 210.1, Version 2. Effective date: 6/19/06
No mention of mpMRI is noted in the NCD that discusses covered prostate screening tests.

No other NCDs were noted.

Local:

There is no local coverage determination. There is a fee schedule for 55706 and 77021.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

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

---

References

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024; 74(1): 12-49. PMID 38230766 Bjurlin MA, Meng X, Le Nobin J, et al. Optimization of prostate biopsy: the role of magnetic resonance imaging targeted biopsy in detection, localization and risk assessment. J Urol. Sep 2014; 192(3): 648-58. PMID 24769030
2. Bjurlin MA, Meng X, Le Nobin J, et al. Optimization of prostate biopsy: the role of magnetic resonance imaging targeted biopsy in detection, localization and risk assessment. J Urol. Sep 2014; 192(3): 648-58. PMID 24769030
3. Hu X, Yang ZQ, Shao YX, et al. MRI-targeted biopsy versus standard transrectal ultrasound-guided biopsy: a systematic review and meta-analysis of randomized controlled trials. Abdom Radiol (NY). Oct 2020; 45(10): 3283-3292. PMID 31897680
4. Tang Y, Liu Z, Tang L, et al. Significance of MRI/Transrectal Ultrasound Fusion Three-Dimensional Model-Guided, Targeted Biopsy Based on Transrectal Ultrasound-Guided Systematic Biopsy in Prostate Cancer Detection: A Systematic Review and Meta-Analysis. Urol Int. 2018; 100(1): 57-65. PMID 29084410
5. Wegelin O, van Melick HHE, Hooft L, et al. Comparing Three Different Techniques for Magnetic Resonance Imaging-targeted Prostate Biopsies: A Systematic Review of In-bore versus Magnetic Resonance Imaging-transrectal Ultrasound fusion versus Cognitive Registration. Is There a Preferred Technique?. Eur Urol. Apr 2017; 71(4): 517-531. PMID 27568655
6. Wu J, Ji A, Xie B, et al. Is magnetic resonance/ultrasound fusion prostate biopsy better than systematic prostate biopsy? An updated meta- and trial sequential analysis. Oncotarget. Dec 22 2015; 6(41): 43571-80. PMID 26498362
7. Schoots IG, Roobol MJ, Nieboer D, et al. Magnetic resonance imaging-targeted biopsy may enhance the diagnostic accuracy of significant prostate cancer detection compared to standard transrectal ultrasound-guided biopsy: a systematic review and meta-analysis. Eur Urol. Sep 2015; 68(3): 438-50. PMID 25480312
8. Elwenspoek MMC, Sheppard AL, McInnes MDF, et al. Comparison of Multiparametric Magnetic Resonance Imaging and Targeted Biopsy With Systematic Biopsy Alone for the Diagnosis of Prostate Cancer: A Systematic Review and Meta-analysis. JAMA Netw Open. Aug 02 2019; 2(8): e198427. PMID 31390032
9. Drost FH, Osses D, Nieboer D, et al. Prostate Magnetic Resonance Imaging, with or Without Magnetic Resonance Imaging-targeted Biopsy, and Systematic Biopsy for Detecting Prostate Cancer: A Cochrane Systematic Review and Meta-analysis. Eur Urol. Jan 2020; 77(1): 78-94. PMID 31326219
10. Haider MA, Brown J, Yao X, et al. Multiparametric Magnetic Resonance Imaging in the Diagnosis of Clinically Significant Prostate Cancer: an Updated Systematic Review. Clin Oncol (R Coll Radiol). Dec 2021; 33(12): e599-e612. PMID 34400038
11. Bass EJ, Pantovic A, Connor MJ, et al. Diagnostic accuracy of magnetic resonance imaging targeted biopsy techniques compared to transrectal ultrasound guided biopsy of the prostate: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis. Feb 2022; 25(2): 174-179. PMID 34548624

12. Tu X, Liu Z, Zhang C, et al. Diagnostic Role of Magnetic Resonance Imaging-Targeted Biopsy for Prostate Cancer in Biopsy-Naïve Men: A Meta-Analysis. Urol Int. 2020; 104(3-4): 187-198. PMID 31825927
13. Klotz L, Chin J, Black PC, et al. Comparison of Multiparametric Magnetic Resonance Imaging-Targeted Biopsy With Systematic Transrectal Ultrasonography Biopsy for Biopsy-Naive Men at Risk for Prostate Cancer: A Phase 3 Randomized Clinical Trial. JAMA Oncol. Apr 01 2021; 7(4): 534-542. PMID 33538782
14. Klotz L, Chin J, Black PC, et al. Magnetic Resonance Imaging-Targeted Versus Systematic Prostate Biopsies: 2-year Follow-up of a Prospective Randomized Trial (PRECISE). Eur Urol Oncol. Jun 2024; 7(3): 456-461. PMID 37838556
15. Eklund M, Jäderling F, Discacciati A, et al. MRI-Targeted or Standard Biopsy in Prostate Cancer Screening. N Engl J Med. Sep 02 2021; 385(10): 908-920. PMID 34237810
16. Wang X, Xie Y, Zheng X, et al. A prospective multi-center randomized comparative trial evaluating outcomes of transrectal ultrasound (TRUS)-guided 12-core systematic biopsy, mpMRI-targeted 12-core biopsy, and artificial intelligence ultrasound of prostate (AIUSP) 6-core targeted biopsy for prostate cancer diagnosis. World J Urol. Mar 2023; 41(3): 653-662. PMID 35852595
17. Hugosson J, Månsson M, Wallström J, et al. Prostate Cancer Screening with PSA and MRI Followed by Targeted Biopsy Only. N Engl J Med. Dec 08 2022; 387(23): 2126-2137. PMID 36477032
18. Ahdoot M, Wilbur AR, Reese SE, et al. MRI-Targeted, Systematic, and Combined Biopsy for Prostate Cancer Diagnosis. N Engl J Med. Mar 05 2020; 382(10): 917-928. PMID 32130814
19. Maxeiner A, Kittner B, Blobel C, et al. Primary magnetic resonance imaging/ultrasonography fusion-guided biopsy of the prostate. BJU Int. Aug 2018; 122(2): 211-218. PMID 29569320
20. Filson CP, Natarajan S, Margolis DJ, et al. Prostate cancer detection with magnetic resonance-ultrasound fusion biopsy: The role of systematic and targeted biopsies. Cancer. Mar 15 2016; 122(6): 884-92. PMID 26749141
21. Siddiqui MM, Rais-Bahrami S, Turkbey B, et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. JAMA. Jan 27 2015; 313(4): 390-7. PMID 25626035
22. Pierorazio PM, Walsh PC, Partin AW, et al. Prognostic Gleason grade grouping: data based on the modified Gleason scoring system. BJU Int. May 2013; 111(5): 753-60. PMID 23464824
23. Antonarakis ES, Feng Z, Trock BJ, et al. The natural history of metastatic progression in men with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up. BJU Int. Jan 2012; 109(1): 32-9. PMID 21777360
24. Eggener SE, Scardino PT, Walsh PC, et al. Predicting 15-year prostate cancer specific mortality after radical prostatectomy. J Urol. Mar 2011; 185(3): 869-75. PMID 21239008
25. Schoots IG, Petrides N, Giganti F, et al. Magnetic resonance imaging in active surveillance of prostate cancer: a systematic review. Eur Urol. Apr 2015; 67(4): 627-36. PMID 25511988
26. Klotz L, Pond G, Loblaw A, et al. Randomized Study of Systematic Biopsy Versus Magnetic Resonance Imaging and Targeted and Systematic Biopsy in Men on Active Surveillance (ASIST): 2-year Post-biopsy Follow-up. Eur Urol. Mar 2020; 77(3): 311-317. PMID 31708295
27. Klotz L, Loblaw A, Sugar L, et al. Active Surveillance Magnetic Resonance Imaging Study (ASIST): Results of a Randomized Multicenter Prospective Trial. Eur Urol. Feb 2019; 75(2): 300-309. PMID 30017404

28. Schiavina R, Droghetti M, Novara G, et al. The role of multiparametric MRI in active surveillance for low-risk prostate cancer: The ROMAS randomized controlled trial. Urol Oncol. Jul 2021; 39(7): 433.e1-433.e7. PMID 33191117
29. Frye TP, George AK, Kilchevsky A, et al. Magnetic Resonance Imaging-Transrectal Ultrasound Guided Fusion Biopsy to Detect Progression in Patients with Existing Lesions on Active Surveillance for Low and Intermediate Risk Prostate Cancer. J Urol. Mar 2017; 197(3 Pt 1): 640-646. PMID 27613356
30. Ma TM, Tosoian JJ, Schaeffer EM, et al. The Role of Multiparametric Magnetic Resonance Imaging/Ultrasound Fusion Biopsy in Active Surveillance. Eur Urol. Feb 2017; 71(2): 174-180. PMID 27236496
31. Da Rosa MR, Milot L, Sugar L, et al. A prospective comparison of MRI-US fused targeted biopsy versus systematic ultrasound-guided biopsy for detecting clinically significant prostate cancer in patients on active surveillance. J Magn Reson Imaging. Jan 2015; 41(1): 220-5. PMID 25044935
32. Walton Diaz A, Shakir NA, George AK, et al. Use of serial multiparametric magnetic resonance imaging in the management of patients with prostate cancer on active surveillance. Urol Oncol. May 2015; 33(5): 202.e1-202.e7. PMID 25754621
33. Gordetsky JB, Saylor B, Bae S, et al. Prostate cancer management choices in patients undergoing multiparametric magnetic resonance imaging/ultrasound fusion biopsy compared to systematic biopsy. Urol Oncol. May 2018; 36(5): 241.e7-241.e13. PMID 29526599
34. Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. J Clin Oncol. Jan 20 2015; 33(3): 272-7. PMID 25512465
35. National Comprehensive Cancer Network. Prostate Cancer. Version 4.2024. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed November 22, 2024.
36. American College of Radiology (ACR). ACR Appropriateness Criteria: Prostate Cancer--Pretreatment Detection, Surveillance, and Staging. 2022. https://acsearch.acr.org/docs/69371/Narrative/. Accessed June 20, 2024.
37. American College of Radiology (ACR). ACR Appropriateness Criteria: Post-treatment Follow-up of Prostate Cancer. 2022. https://acsearch.acr.org/docs/69369/Narrative/. Accessed June 21, 2024.
38. National Institute for Health and Care Excellence. Prostate cancer: diagnosis and management. https://www.nice.org.uk/guidance/ng131. Accessed June 25, 2024.
39. Rosenkrantz AB, Verma S, Choyke P, et al. Prostate Magnetic Resonance Imaging and Magnetic Resonance Imaging Targeted Biopsy in Patients with a Prior Negative Biopsy: A Consensus Statement by AUA and SAR. J Urol. Dec 2016; 196(6): 1613-1618. PMID 27320841
40. Bjurlin MA, Carroll PR, Eggener S, et al. Update of the Standard Operating Procedure on the Use of Multiparametric Magnetic Resonance Imaging for the Diagnosis, Staging and Management of Prostate Cancer. J Urol. Apr 2020; 203(4): 706-712. PMID 31642740
41. National Comprehensive Cancer Network. Prostate Cancer Early Detection. Version 2.2024. https://www.nccn.org/professionals/physician_gls/pdf/prostate_detection.pdf. Accessed November 22, 2024.
42. Centers for Medicare & Medicaid Services. Prostate cancer screening tests. 2006. https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=268&ncdver=2&bc=0. Accessed November 22, 2024.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through November 22, 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/24	2/28/24		• Joint policy established (slp) • Vendor managed: N/A
5/1/25	2/18/25		• Joint policy established (slp) • Vendor managed: N/A

Next Review Date: 1st Qtr, 2026

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: MAGNETIC RESONANCE IMAGING – TARGETED BIOPSY OF THE PROSTATE

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.
- *Duplicate (back-up) equipment is not a covered benefit.*