Magnetic Resonance Imaging–Targeted Biopsy of the Prostate

Policy # 00492
Original Effective Date: 03/16/2016
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Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers magnetic resonance imaging (MRI)–targeted biopsy of the prostate to be investigational.*

Background/Overview
Magnetic resonance imaging allows for targeted biopsy of suspicious lesions in the prostate, rather than blind biopsy, as is done with the current standard of care, transrectal ultrasound (TRUS)–guided biopsy. The use of MRI-guided prostate biopsy may identify areas in the prostate that harbor high-grade tumor, minimizing the detection of clinically insignificant cancers and possible overtreatment and distinguishing men more appropriately managed by active surveillance from men recommended for definitive intervention.

Prostate biopsy typically is performed in men who have an elevated prostate-specific antigen (PSA) level or who present with symptoms. The purpose of the biopsy is to determine whether cancer is present and to determine tumor grade. Tumor grade (Gleason score) is a major determinate in whether a patient is eligible for active surveillance (lower grade tumors) or factor for determining definitive intervention (higher grade tumors).

Biopsies to diagnose prostate cancer are currently performed using 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. Prior to the 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 miss diagnosis of clinically significant disease. Compared with subsequent prostatectomy, TRUS underestimates tumor grade up to 40% of the time and too often detects clinically insignificant disease.

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

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

Multiparametric magnetic resonance imaging (mpMRI) includes anatomic T2-weighted imaging for localization of the normal gland and cancer foci and 2 functional imaging techniques: diffusion-weighted and perfusion imaging. The mpMRI 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. Degree of intensity decrease differs with Gleason score; higher Gleason score prostate cancer shows lower signal intensities.1 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 allows assessment of contrast kinetics in focal lesions; prostate cancer typically enhances faster and to a greater extent than the surrounding prostate; however, 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 (US) 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. To date, no prospective comparison of the 3 methods has been made. Based on MRI, suspicious areas are identified (ie, regions of interest) and subjected to targeted biopsy.

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

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

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

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

**FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)

Magnetic resonance imaging-guided or MRI/ultrasound (US) fusion biopsy is a medical procedure that uses MRI and ultrasound devices previously approved by the FDA. Prostate biopsy is a surgical procedure and, as such, it is not subject to regulation by 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 from marketing by FDA through the 510(k) marketing process. Fusion software and (manufacturers) include: Artemis TM (Eigen), BioJet TM (D&K Technologies), BiopSee TM (MedCom), Real-time Visual Sonography (Hitachi), UroNav TM (Invivo/Philips), Urostation TM (Koelis), and Virtual Navigator (Esaote).

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**Rationale/Source**

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

A 2015 systematic review and meta-analysis by Schoots et al (search through May 2014) assessed the diagnostic differences between MRI–targeted biopsy (MRI-TBx) and TRUS–guided biopsy (TRUS-Bx) in detecting overall prostate cancer (primary objective) and clinically significant and insignificant prostate cancer (secondary objective). Selected studies included men with suspected prostate cancer scheduled for transrectal biopsy because of increased prostate-specific antigen and/or positive digital rectal exam. Overall, according to QUADAS criteria, the methodologic quality of the studies was deemed to be fair. Only studies that included both MRI-TBx and conventional TRUS-Bx in each patient were included in order to compare the 2 technologies. Therefore, all men had a positive MRI, defined as a suspicious lesion on prostate MRI scan. Reports on transperineal or saturation biopsy were excluded. Relative sensitivity was the sensitivity ratio between MRI-TBx and TRUS-Bx. A relative sensitivity of greater than 1 indicated that MRI-TBx detected more cancers than TRUS-Bx, and a relative sensitivity less than 1 indicated that MRI-TBx detected fewer cancers than TRUS-Bx. Analyses were performed for 2 predefined subgroup categories: patient population was categorized as men undergoing initial biopsy, men with a previous negative biopsy, and reports in which results were mixed for initial versus subsequent biopsy; and navigational system for MRI as direct versus fusion biopsy with visual or software registration. Sixteen studies with 1926 men were eligible. MRI-TBx and TRUS-Bx did not differ significantly in overall prostate cancer detection (sensitivity, 0.85; 95% confidence interval [CI], 0.80 to 0.89 vs sensitivity, 0.81; 95% CI,
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0.70 to 0.88, respectively). Ten studies presented data on the detection of significant versus insignificant prostate cancer detection. Of the 10 studies, 5 reported results for initial biopsy, 2 for a previous negative biopsy, and 3 with a mixed population. MRI-TBx had a higher rate of detection of significant prostate cancer than TRUS-Bx (sensitivity, 0.91; 95% CI, 0.87 to 0.94 vs sensitivity, 0.76; 95% CI, 0.64 to 0.84) and a lower rate of detection of insignificant prostate cancer (sensitivity, 0.44; 95% CI, 0.26 to 0.64 vs sensitivity, 0.83; 95% CI, 0.77 to 0.87). The improvement in significant prostate cancer detection by MRI-TBx was in men with previous negative biopsy, but not 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). Two of 16 studies reported mixed data on MRI-visual-TBx and MRI-fusion-TBx. Therefore, 14 studies were available to compare outcomes of one navigational system versus another, of which only 8 presented data on the detection of significant and insignificant prostate cancer: 2 studies with MRI-visual-TBx, 5 with MRI-fusion-TBx, and 1 with MRI-in-bore-TBx. MRI-fusion-TBx and MRI-in-bore-TBx significantly improved prostate cancer detection compared with TRUS-Bx (relative sensitivity, 1.29; 95% CI, 1.16 to 1.43 vs relative sensitivity, 1.26; 95% CI, 1.08 to 1.46, respectively). MRI-visual-TBx did not show much improvement compared with TRUS-Bx (relative sensitivity, 1.03; 95% CI, 0.91 to 1.16).

In summary, the study found that MRI-TBx had a 20% better detection rate for clinically significant prostate cancer than TRUS-Bx. A relative sensitivity of 0.56 was found for detection of insignificant prostate cancer, in that MRI-TBx showed an almost twofold better performance in avoiding detection of insignificant prostate cancer than TRUS-Bx. Strengths of this meta-analysis included the focus on reports that included comparison of biopsies performed by both MRI-guided and TRUS biopsy in the same patient. Limitations included the inclusion of small studies and publication bias, because the studies only included patients with a positive MRI.

A 2015 systematic review by Valerio et al (search through December 2013) compared the detection rate of clinically significant cancer with software-based MRI-US fusion biopsy versus standard TRUS biopsy. Secondary outcomes were detection rate of all cancer, sampling efficiency, and utility and rate of serious adverse events. Fourteen articles were included in the final analysis. Most studies were considered to have a low risk of bias and low concern for applicability with respect to patient selection. Two studies were scored as potentially biased; one had a small sample size (n=13) and significant patient heterogeneity, and the other had a retrospective design and patient heterogeneity. All but 1 study were paired cohort design. Thirteen studies used 10- to 12-core TRUS biopsy as the reference test; 1 study used transperineal biopsy, however, systematic transperineal template cores were not taken from areas previously mapped using MRI-TRUS fusion biopsies and, therefore, the detection rate of clinically significant disease could not be compared. A total of 2293 men were included in the review, with sample sizes ranging from 13 to 582. Three studies were conducted in men undergoing first biopsy, 3 in men with a previous negative TRUS biopsy, 8 studies in a mixed cohort with either first biopsy or a previous biopsy, and 1 study with men with recurrent disease post radiation. Median detection of clinically significant cancer was 23.6% (range, 4.8%-52%) for standard biopsy and 33.3% (range, 13.2%-50%) for MRI-TRUS fusion-targeted biopsy. Only 1 study did not report the criteria for defining clinically significant disease. In the remaining studies, the presence of Gleason pattern 4 was considered to be clinically significant disease. For secondary outcomes, median detection rate of any cancer was 43.4% for standard biopsy (range, 14.3%-59%) and 50.5% (range, 23.7%-82.1%) for MRI-TRUS fusion biopsy. Median number of cores needed to detect clinically significant
cancer was 37.1 and 9.2 for standard and MRI-TRUS fusion-targeted biopsy, respectively. Utility, defined as the number of clinically significant cancers detected by 1 strategy but missed by the other, was an absolute difference of 9.1% (range, 5%-16.2) in favor of the MRI-TRUS biopsy.

Limitations of the review included heterogeneity in study design and patient population, and variability across studies in terms of MRI characteristics and interpretation, threshold for biopsy, targeted biopsy conduct, and number of cores per target.

**MRI-Guided Biopsy in Active Surveillance**

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

Ten publications assessed radical prostatectomy data from men on active surveillance who had undergone preoperative MRI. Of men who chose surgery, 152 of 1070 (14%) were upstaged to T3 disease or worse, and 163 of 353 (43%) were upgraded to a Gleason score greater than 6. The likelihood of a positive MRI preoperatively was 73% (963/1326). Upgrading occurred in 43% (291/677) of cases with a positive preoperative MRI versus 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 8% (16/194) with a negative MRI.

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

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this policy are listed in Table 1.

Table 1. Summary of Key Trials

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<td>NCT01883128</td>
<td>An Evaluation of a Novel Imaging Based Complex Diagnostic and Therapeutic Pathway Intervention for Men Who Fail Radiotherapy for Prostate Cancer</td>
<td>177</td>
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<td>NCT02242773</td>
<td>MRI-Guided Biopsy Selection of Prostate Cancer Patients for Active Surveillance Versus Treatment: The Miami MAST Trial</td>
<td>165</td>
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NCT: national clinical trial.

Summary of Evidence
The evidence for the use of magnetic resonance imaging‒targeted diagnostic or surveillance biopsy of the prostate includes numerous prospective and retrospective studies of paired cohorts and systematic reviews and meta-analyses of these studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy, morbid events, and quality of life. Systematic reviews of the use of MRI-guided prostate biopsy have shown the technology may diagnose more high-grade cancers than TRUS biopsy and fewer low-grade cancers, which may stratify patients for treatment versus active surveillance. In active surveillance, it has not been shown that this technique can detect patients who have progressed and need definitive intervention. It is unknown whether use of this technique will translate into positive clinically meaningful outcomes in terms of survival or quality of life. Further prospective evaluation of MRI-guided techniques is needed to determine whether this approach results in improved health outcomes, whether this approach would replace the standard biopsy protocol, or whether it would be performed in addition to TRUS-guided biopsy. The evidence is insufficient to determine the effects of the technology on health outcomes.

References
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03/03/2016 Medical Policy Committee review
03/16/2016 Medical Policy Implementation Committee approval. New Policy.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
03/02/2017 Medical Policy Committee review
03/15/2017 Medical Policy Implementation Committee approval. No change to coverage.
Next Scheduled Review Date: 03/2018

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

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