MEDICAL POLICY	Prostate: MRI-Transrectal Ultrasound (MRI-TRUS) Fusion Biopsy
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See Policy CPT CODE section below for any prior authorization requirements

SCOPE:

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:

All lines of business

BENEFIT APPLICATION

Medicaid Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

POLICY CRITERIA

I. The use of MRI-transrectal ultrasound (MRI-TRUS) fusion to guide prostate cancer biopsy may be considered **medically necessary** when **either** of the following criteria are met (A. or B.):

A. For diagnosis when **both** of the following are met (1-2):
    1. One or more prior negative TRUS biopsy; **and**
    2. Repeat digital exam concerning for progression of disease and/or rising PSA. **or;**

B. For active surveillance when **all** of the following are met (1. – 4.):
    1. Life expectancy > 5 years; **and**
    2. MRI result is suspicious for intermediate/high risk prostate cancer; **and**
    3. Repeat digital exam concerning for progression of disease and/or rising PSA; **and**
    4. Repeat biopsy is performed in support of changes in treatment or in support of definitive treatment.

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II.   The use of MRI-TRUS fusion to guide prostate cancer biopsy is considered **investigational*** **and is not covered** when the above criterion I. is not met, including, but not limited to the initial biopsy.

*Investigational services are considered "not medically necessary" for Medicare Plan members. Link to Centers for Medicare and Medicaid Services (CMS).

Link to Policy Summary

CPT CODES

All Lines of Business	
Prior Authorization Required	
72195	Magnetic resonance (eg, proton) imaging, pelvis; without contrast material(s)
72196	Magnetic resonance (eg, proton) imaging, pelvis; with contrast material(s)
72197	Magnetic resonance (eg, proton) imaging, pelvis; without contrast material(s), followed by contrast material(s) and further sequences
76376	3D rendering with interpretation and reporting of computed tomography, magnetic resonance imaging, ultrasound, or other tomographic modality with image postprocessing under concurrent supervision; not requiring image postprocessing on an independent workstation
No Prior Authorization Required	
55700	Biopsy, prostate; needle or punch, single or multiple, any approach
76872	Ultrasound, transrectal
76942	Ultrasonic guidance for needle placement (eg, biopsy, aspiration, injection, localization device), imaging supervision and interpretation
77021	Magnetic resonance guidance for needle placement (eg, for biopsy, needle aspiration, injection, or placement of localization device) radiological supervision and interpretation
Unlisted Codes All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then **prior-authorization is required.**	
55899	Unlisted procedure, male genital system
76498	Unlisted magnetic resonance procedure (eg, diagnostic, interventional)

DESCRIPTION

Prostate Cancer

In the United States, prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer death in men. Prostate cancer is more common in older men and men of African

American ethnicity. Approximately 1 in 7 men will be diagnosed with prostate cancer in his lifetime. In 2018, it is estimated that 164,690 men will be diagnosed with prostate cancer and 29,430 will die of the disease in the United States.[1]

Although almost all prostate cancers are adenocarcinomas, there are several other types of prostate cancer, including sarcomas, small cell carcinomas, neuroendocrine tumors and transitional cell carcinomas.[1] Prostate cancer is a heterogeneous disease with tumors ranging from indolent to very aggressive. Survival differs according to disease stage at diagnosis. The majority of prostate cancers are discovered prior to becoming metastatic and therefore the 5-year relative survival rate is close to 100%. However, men with metastatic disease have a 5-year survival rate of approximately 30%.[2]

Prostate Cancer Detection

Prostate cancer is commonly identified in asymptomatic men by routine screening that includes measuring levels of prostate-specific antigen (PSA) in blood and via digital rectal examination (DRE). When initial testing results are suspicious for prostate cancer, a prostate biopsy is warranted.[3]

Imaging Modalities

Transrectal Ultrasonography (TRUS) Biopsy

Transrectal ultrasonography (TRUS)-guided needle biopsy currently provides the definitive diagnosis for prostate cancer.[4] It may also be used to monitor disease progression in patients undergoing active surveillance. For this technique, TRUS is employed to generate images of the prostate and guide needle placement. During TRUS-guided biopsy, the prostate is systematically sampled and 10-12 needle cores are obtained. Due to the systematic, nontargeted nature of this biopsy method, there is a chance of false-negative results.

Although TRUS biopsy is considered the standard to diagnose prostate cancer, 20-30% may yield false negative results due, in part, to poor tissue sampling during biopsy that has missed localized lesions. As a result, a large proportion of patients with an initial negative biopsy may undergo repeat biopsy if there is a suspicion of prostate cancer based on other clinical factors. Therefore, confirming the presence or absence of prostate cancer is an area of major clinical interest.[5]

A number of emerging imaging modalities are currently being evaluated in an effort to improve detection of clinically significant cancer and reduce the number of repeat biopsies.

Multiparametric Magnetic Resonance Imaging (mpMRI)

Multiparametric magnetic resonance imaging (mpMRI) has recently gained attention for its ability to provide more detailed images of prostate lesions. mpMRI has multiple applications for prostate cancer. It is used to characterize tumors, guide biopsies, conduct active surveillance, and detect local recurrence following prostatectomy.[4]

mpMRI consists of three components: T2-weighted magnetic resonance (MR) images; and ≥ 2 functional MRI sequences, including diffusion weighted imaging (DWI) and either dynamic contrast enhanced (DCE)

MRI or spectroscopic imaging (MRSI). The images obtained from mpMRI can be used to target TRUS biopsies in one of three ways:[4,6]

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1. MRI-TRUS fusion:
   - Software is used to overlay a previous MRI image with a real-time TRUS using a fusion device. This digital overlay allows for aiming and tracking of the biopsy site.
   - This approach is the focus of this medical policy and is described in more detail below.

2. Direct MRI-guided biopsy (also referred to as "in-bore"):
   - A transrectal biopsy is performed when patient is in the MRI scanner. The radiologist fuses a previous MRI image with a contemporaneous MRI to localize needle and sample the target areas only.

3. Cognitive fusion (also referred to as visual fusion):
   - Prior to biopsy, an MRI demonstrates a lesion. The TRUS operator reviews the MRI and manually aims the biopsy needle to the location where the lesion appears to be located. Studies indicate that this approach is inferior to other MRI-targeted biopsy approaches.

NOTE: The direct "in-bore" MRI-guided biopsy and the cognitive fusion biopsy approaches are beyond the scope of this medical policy and will not be addressed further.

MRI-TRUS Fusion biopsy

MRI-TRUS fusion biopsy, also called targeted biopsy, or 3-D ultrasound-guided prostate biopsy, is performed using fusion devices that utilize software to align a pre-biopsy MRI with a live intraoperative TRUS. This allows a TRUS biopsy to be performed while directing the needle toward lesions that are visible on the MRI.

During the MRI-TRUS fusion biopsy, mpMRI images are loaded to the MRI-TRUS fusion software, and suspicious lesions are outlined. The patient is then positioned for a TRUS, and the software aligns (coregisters) the annotated MRI image with the real-time TRUS image.

According to Hayes, "MRI-TRUS fusion devices coregister MRI and intraoperative TRUS images using 1 of 2 methods: rigid or non-rigid (elastic) registration. Each type of coregistration identifies landmarks present in both images to achieve alignment. Rigid coregistration does not permit changes to the images themselves, and allows only rotational and translational variations between images. With this type of coregistration, the urologist must manually correct any errors in alignment and targeting. Conversely, elastic registration allows for dimensional changes and warping between images, which are based on mathematical algorithms. It is not currently clear which method is more accurate. Following image alignment, the urologist or radiologist will perform a targeted TRUS biopsy directed toward the lesion(s) identified on the mpMRI."[4]

While MRI-TRUS fusion imaging for biopsy guidance has the potential to reduce the number of men undergoing biopsy and the detection of indolent disease, it is also prone to false negative results. MRI-TRUS fusion will miss clinically significant cancers that fall outside of the area of detection.[3] Furthermore, the mpMRI imaging of the prostrate, prior to fusion, has been reported to miss clinically significant tumors and underestimated tumor size and volume.[7] In addition, differences in MRI scanners and digital systems for image fusion, as well as operator experience may lead to differences in results. Continued trials are expected improve these shortcomings.

REVIEW OF EVIDENCE

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of MRI-TRUS fusion biopsy as a modality for the diagnosis and management of prostate cancer. Below is a summary of the available evidence identified through February 2022.

A number of recent systematic reviews of MRI-TRUS fusion biopsy have been published which address both biopsy-naïve patients and patients with a prior biopsy. These are described in detail below. In addition, the use of MRI-TRUS fusion biopsy in these patient subpopulations have been published separately in the form of RCTs and large nonrandomized studies. Key studies included in the recent reviews, as well as RCTs and nonrandomized studies published after the systematic reviews are also described in detail below, by patient population.

Prostate Cancer Diagnosis

Systematic Reviews Including Mixed Patient Populations

- In 2014 (updated 2018), ECRI conducted an evidence review evaluating magnetic resonance/ultrasound fusion biopsies for diagnosing prostate cancer.[8] Searching the literature through August 2018, investigators ultimately included 7 studies for review (1 systematic review, 1 cohort study, 2 RCTs, 2 case series). Outcomes of interest included diagnostic yields of systematic biopsy and MRI/US-fusion-targeted biopsy in patients with suspected prostate cancer, and cancer progression detection. Results assessing clinical validity across studies were mixed. The systematic review reported that MRI/US fusion did not improve active surveillance of low-risk prostate cancer in one RCT (n=296) but did identify additional high-risk tumors in 16% of patients undergoing systematic biopsy in one prospective diagnostic cohort study (n=1,042). One RCT (n=210) reported less pain and shorter procedures for MRI/US fusion than with in-bore MRI biopsy, while case series found that MRI/US-fusion-targeted and systematic biopsy prompted treatment changes in 13% to 38% more patients than systematic biopsy alone. Findings were limited by studies' retrospective design, heterogeneous patient populations, heterogenous MRI criteria, and lack of data evaluating patient outcomes. ECRI concluded that meta-analysis of available data and prospective studies reporting on patient outcomes were needed.

- In 2015 (archived in 2021), a Hayes review was published on the use of MRI-TRUS fusion-guided biopsy for the diagnosis of prostate cancer, including 16 studies.[4] The studies included nine prospective cohort studies, four retrospective reviews (three of prospective studies) and

two RCTs. Study designs differed in whether all patients had both MRI-TRUS fusion biopsy as well as the comparator, and there was variation in methods for calculating detection rates. Most of the studies were unblinded or had potential for unblinding due to the ability to observe the location of previous biopsies. All studies were pooled together regardless of previous biopsy history and subgroup analyses were not performed. The overall quality of the evidence was deemed low for MRI-TRUS fusion biopsy to diagnose prostate cancer, ranging from very low to moderate for each endpoint. For this reason, MRI-TRUS fusion biopsy was given a rating of "C" for men suspected of having prostate cancer based on either an elevated prostate-specific antigen (PSA) level and/or enlarged prostate, or MRI-suspicious lesions. The Hayes review concluded that although evidence suggests that MRI-TRUS fusion-guided biopsy may detect more clinically significant cancers and fewer clinically insignificant cancers compared with standard biopsy, there are uncertainties regarding optimal methodology, definition of clinical significance, patient selection criteria, and outcomes related to clinical utility.

In addition to primary literature, the Hayes review also included five recent systematic reviews published on the use of MRI-TRUS fusion biopsy for diagnosing prostate cancer. [9-13] Subgroup analyses of MRI-TRUS and TRUS-only biopsies in these systematic reviews generally reported similar detection levels of overall cancer between the two biopsy methods the initial biopsy setting (62% for MRI-TRUS versus 65% for TRUS-alone, p=0.16).[11] However, in the setting of previous negative initial biopsy, MRI-TRUS showed improved overall cancer detection compared to TRUS-alone (37% versus 24%, respectively, p=0.001). In addition, MRI-TRUS showed higher detection of significant cancer in men with a previous negative biopsy compared to men undergoing initial biopsy. Furthermore, MRI-TRUS biopsy showed lower detection of insignificant prostate cancers in men with an initial biopsy compared to men with a previous negative biopsy. These reviews had a number of limitations themselves, including significant heterogeneity in patient inclusion between studies, definitions of clinically significant cancer, and protocols used to conduct standard biopsies. These reviews also suffered from inclusion of a limited number of moderate to good quality studies. Overall, these systematic reviews suggest MRI-TRUS fusion biopsy may have higher detection rates for clinically significant prostate cancer. These higher detection rates are more consistent among repeat biopsy patients and not as well established for biopsy-naïve patients.

- In 2020, Hu and colleagues published a systematic review and meta-analysis on MRI-targeted biopsy (MRI-TBx) versus standard transrectal ultrasound-guided biopsy (TRUS-Bx).[14] The review included 8 RCTs comprising of 2593 patients. Six studies included patients without previous biopsy, and 2 studies included patients with prior negative biopsy. Detection rates of overall prostate cancer in the MRI-TBx (57.1%) were higher than the TRUS-Bx group (38.8%), but the differences were not significantly different (RR = 1.30; 95% CI 0.98–1.72; P = 0.067; I^2 = 87.5%). Five studies including 1200 patients analyzed clinically significant versus insignificant prostate cancer diagnoses. The detection rate of clinically significant prostate cancer in the MRI-TBx group was 37.5% versus 27.6 percent in the TRUS group, a non-significant difference (RR = 1.35; 95% CI 0.98–1.86; P = 0.065; I^2 = 70.6%). Similarly, there was no significant difference in clinically insignificant prostate cancer diagnosis between the two groups (RR = 0.76; 95% CI 0.40–1.46; P = 0.416; I2 = 68.8%).

A subgroup analysis was conducted based on initial biopsies. In patients with initial biopsy, MRI-TBx had a significantly higher detection rate of overall prostate cancer detection (RR = 1.40; 95% CI 1.01–1.94; P = 0.045). The detection rates of clinically significant and insignificant PCa between MRI-TBx and TRUS-Bx did not differ significantly. In patients with previous negative biopsy, the detection rates of overall, clinically significant and insignificant PCa did not significantly differ between the groups. This study held a number of limitation. Only 8 trials were included, and analyses on clinically significant diagnoses and subgroup analyses on initial biopsy had smaller sample sizes still. All but one of the RCTS was single-centered, potentially leading to biases. Clinically significant prostate cancer definitions differed between studies, and there was significant heterogeneity among the RCTs. The authors concluded that MTI-TBx potentially benefits the detection of overall and clinically significant prostate cancer compared with TRUS-Bx in patients with a suspicion of PCa. They suggest that more large, multicenter RCTs be conducted to determine MRI targeted therapy was an initial biopsy and for those with previously negative biopsies.

Primary studies published after the publication of the Hayes systematic review are described below.

Studies of Patients with Mixed Biopsy Indications

- In 2016, Filson et al. reported the results of a single-center prospective study that evaluated the performance of MRI-US-guided fusion biopsy in detecting clinically significant prostate cancer (csPCa, defined as Gleason score ≥7), including 1042 men.[15] Biopsy-naïve patients (n=329), patients with a prior negative biopsy (n=324) and patients undergoing active surveillance with a prior positive biopsy (n=389), were included. In a combined analysis, 825 (79%) patients had at least one region of interest (ROI) of grade 3 or more, and of these patients 289 (35%) were found to have csPCa through combination of MRI-TRUS fusion and TRUS-guided biopsy (combined biopsy). The number of csPCa cases identified by combined biopsy were significantly higher than cases identified by either MRI-TRUS fusion only (229 cases; p<0.001) or by systematic biopsy (199 cases; p<0.001). Based on the results, the authors calculated the negative predictive value (NPV) of 56% for any cancer and 85% for csPCa, which is within the range of NPVs for mpMRI published in a recent meta-analysis (NPVs ranged from 65-94%).[9] This suggests that a negative mpMRI should not routinely replace standard biopsy as a method to rule out the presence of csPCa.

  Of note, subgroup analyses of cancer detection stratified by biopsy indication (biopsy-naïve, prior negative, and prior positive biopsy) were performed. In patients that had a maximum ROI of grade 4 or more, MRI-TRUS biopsies consistently detected a greater percentage of csPCa for all biopsy groups. However, no statistical analyses were performed, so it is unclear if the differences in each biopsy group where significant. One limitation of this study was the use of institution-specific protocols for grading of ROIs that varied slightly from the validated PI-RADS grading scheme. This deviation may limit generalizability to other practice settings.

- In 2020, Benelli and colleagues published results of a retrospective study evaluating the role of MRI/TRUS fusion biopsy in the diagnosis of clinically significant prostate cancer in biopsy-naïve patients and in patients in active surveillance protocols.[16] A total of 416 patients were enrolled in the study, 236 (56.7%) of which had a previous negative systematic biopsy. In biopsy-naïve

patients, 47 (34.8%) were found to have a clinically significant prostate cancer diagnosis. Among patient in active surveillance, 17 (43.6%) were found to have clinical significant prostate cancer diagnoses. This trial was limited in that it did not include a comparator group, was retrospective in design, collected data from a single institution, and there was no blinding. The authors conclude that the MRI/TRUS fusion prostate biopsy is emerging as a significant diagnostic tool for biopsy-naïve patients, but further studies are necessary.

Initial Biopsy

Randomized Controlled Trials (RCTs)

In 2016, Baco et al. published the results of an RCT that compared the rate of detection of clinically significant PCa (csPCa) between prostate biopsy guided by computer-assisted fusion of MRI and TRUS images (MRI group) and the traditional 12-core random biopsy (RB; control group), including 175 biopsy-naïve patients with suspicion for PCa.[17] In the MRI group, 2-core targeted biopsy (TB) guided by computer-assisted fusion of MRI-TRUS images of MRI-suspicious lesions was followed by 12-core RB. In the control group, both 2-core TB for abnormal DRE and/or TRUS-suspicious lesions and 12-core RB were performed. In patients with normal MRI or DRE/TRUS, only 12-core RB was performed. Detection rates for any cancer (MRI group 51/86, 59%; control group 48/89, 54%; p = 0.4) and csPCa (38/86, 44% versus 44/89, 49%; p = 0.5) did not significantly differ between the groups. Detection of csPCa was comparable between 2-core MRI-TRUS-TB (33/86, 38%) and 12-core RB in the control group (44/89, 49%; p = 0.2). In a subset analysis of patients with normal DRE, csPCa detection was similar between 2-core MRI-TRUS-TB (14/66, 21%) and 12-core RB in the control group (15/60, 25%; p = 0.7). Among biopsy-proven csPCas in MRI group, 87% (33/38) were detected by MRI-TRUS-TB. The authors concluded that overall csPCa detection was similar between the MRI and control groups; 2-core MRI-TRUS-TB was comparable to 12-core RB for csPCa detection. The authors noted that there are still many issues with MRI-TRUS imaging, including low sensitivity of MRI in detecting clinically significant cancer, lack of standardization in MRI-TRUS image-fusion biopsy technique and varied education of urologic practitioners.

In 2016, Tonttila et al. published the results from a single-center, prospective RCT that compared 2-core MRI-TRUS-fusion targeted biopsy with routine TRUS-guided random biopsy for overall and clinically significant PCa detection among 130 biopsy-naive patients with suspected PCa based on PSA values.[2] The overall PCa detection rate and the clinically significant cancer detection rate were similar between the mpMRI and control groups, respectively (64% [34 of 53] versus 57% [34 of 60]; 7.5% difference [95% CI: -10 to 25], p = 0.5, and 55% [29 of 53] versus 45% [27 of 60]; 9.7% difference [95% CI: -8.5 to 27], p = 0.8). The authors noted that the study was underpowered and that based on methodological study limitations, that the true prevalence of clinically significant prostate cancer in the MRI group was unknown. The investigators concluded that MRI-TRUS-fusion targeted biopsy did not improve PCa detection rate compared with TRUS-guided biopsy alone in patients with suspected PCa based on PSA values.

In 2017, Porpiglia et al. published a single-center RCT in Italy among 212 biopsy-naive patients with suspected prostate cancer (elevated PSA but negative DRE).[18] Patients were randomized to a prebiopsy multiparametric MRI (mpMRI) group (n=107) or a standard biopsy group (n=105). The mpMRI was performed with a 1.5-Tesla scanner and endorectal coils were used. Patients in mpMRI group

underwent MRI-TRUS fusion biopsy if they had mpMRI evidence of suspected prostate cancer lesions (n=81); others in this group underwent standard biopsy (n=26). In the as-treated analysis, the MRI-TRUS fusion biopsy approach had a significantly higher detection rate (vs those undergoing standard biopsy from mpMRI group or the standard biopsy group) of overall prostate cancer (61% vs 19% vs 30%, respectively; p<0.001) and for clinically significant prostate cancer (57% vs 4% vs 18%, respectively; p<0.001), however, these significant results must be interpreted with caution, since the different biopsy approach subgroups were not adequately powered. Author-noted limitations of this trial include "lack of correlation with specimen pathology and clinically significant cancer, and heterogeneity of the mpMRI equipment". Although this study reported significantly higher detection of prostate cancer as a result of using MRI-TRUS targeted biopsy, these results conflict with the two similarly sized RCTs published in 2016, which did not find any advantage to incorporating MRI into the biopsy.

A recent multicenter non-inferiority trial also reported comparing the use of MRI-TRUS fusion biopsy to standard 10- 12-core biopsy, recruiting biopsy-naïve patients from 25 centers in 11 countries.[19] While the trial reported positive results, it suffered from a number of limitations, including variability in MRI scanners used between centers, variability in operator experience, inclusion of both academic and non-academic centers, optional use of an endorectal coil. "Also, various techniques of MRI-targeted biopsy, with visual registration or software-assisted registration with either transrectal or transperineal access routes, were permitted." Of note, there was only 78% concordance between the testing site and the central radiologist, indicating inconsistent reporting among operators and a need for improvements to the standardization, reproducibility, and reporting of mpMRI.

Nonrandomized Studies

In 2015, Siddiqui et al. published a large prospective cohort study that compared MRI-TRUS fusion-guided biopsy with TRUS-guided biopsy for the diagnosis of prostate cancer, including 1003 men.[20] Patients were referred for elevated level of prostate-specific antigen (PSA) or abnormal DRE. Targeted MRI-TRUS fusion biopsy diagnosed 461 prostate cancer cases, and standard biopsy diagnosed 469 cases. There was exact agreement between targeted and standard biopsy in 690 men (69%) undergoing biopsy. Targeted biopsy diagnosed 30% more high-risk cancers vs standard biopsy (173 vs 122 cases, P < 0.001) and 17% fewer low-risk cancers (213 vs 258 cases, p < 0.001). When the ability of preoperative biopsy to predict whole-gland pathology was examined, the sensitivity of targeted biopsy was 77% vs 53% for standard biopsy while the specificities were similar (targeted, 68%, vs standard, 66%). The AUC for targeted biopsy (0.73) was significantly greater than that of standard biopsy (0.59, p = 0.005) However, the authors concluded that future studies will be needed to assess the ultimate clinical implications of targeted biopsy. Limitations of this study included the fact that most of the patients had undergone previous biopsies and very few were biopsy-naïve; the study only took place at single institution, and patients with no lesions visible on MP-MRI were excluded from the study. These limitations may have introduced bias and indicate a potential lack of generalizability of the reported efficacy of MRI-TRUS guided technique to the general population. A similar nonrandomized trial published a few years earlier reported similar results, but suffered from a number of limitations similar to the Siddiqui study.[21]

In 2017, Ahmed et al. published a multicenter paired-cohort validation study that evaluated the diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS), comparing it against a reference test (template prostate mapping biopsy [TPM-biopsy]) in 576 men.[22] Men with PSA

up to 15 ng/mL, with no previous biopsy, underwent 1.5T MP-MRI followed by both TRUS-biopsy and TPM-biopsy. The conduct and reporting of each test was done blind to other test results. For clinically significant cancer, MP-MRI was more sensitive (93%, 95% CI 88-96%) than TRUS-biopsy (48%, 42-55%; p<0·0001) and less specific (41%, 36-46% for MP-MRI vs 96%, 94-98% for TRUS-biopsy; p<0·0001). The investigators reported that in TRUS-biopsies directed by MP-MRI findings, up to 18% more cases of clinically significant cancer might be detected compared with the standard TRUS-biopsy.

Additional nonrandomized studies have been published, however, these are limited by heterogeneous patient populations and subgroup analysis that were insufficiently powered to draw meaningful conclusions.[23,24]

Repeat Negative Biopsy

Nonrandomized Studies

Since the publication of the systematic reviews described above, detection of clinically significant cancer rates using MRI-TRUS fusion biopsy have also been reported in recent case series, such as that study published by Simmons et al..[25] This 2017 series of 249 men undergoing repeat biopsy reported that fusion biopsy revealed clinically significant cancer in 103 (41%) of men. Conversely, Boesen et al. recently published the results of a case series of 194 men in order to evaluate the performance of MRI-TRUS biopsy as a method of ruling out prostate cancer in patients with an initial negative biopsy.[26] At follow-up, cancer was detected in 38 of 194 (20%) patients during the median study period of 47 months and an overall negative predictive value of MRI in ruling out significant prostate cancer of 95% (184 of 194).

Active Surveillance

Systematic Reviews

In 2018, Schoots et al. conducted a systematic review that evaluated the additional value of MRI and MRI-targeted biopsies to systematic TRUS biopsies in identifying high-grade prostate cancer in men with low-risk disease.[27] This review included six single center studies (n=1159 men under first re-biopsy 6-24 months after diagnosis) with overall methodological quality determined to be fair to good. The review reported that cancer upgrading (Gleason ≥3+4) occurred in 27% (95%CI: 22-34%) using a combined approach of MRI targeted biopsies and systematic TRUS biopsies. In addition, 35% (95%CI: 27-43%) of men with a positive MRI were upgraded, compared to 12% (95%CI: 8-18%) of men with a negative MRI being upgraded (RR 2.77 [95%CI: 1.76-4.38]). In men with low risk prostate cancer on active surveillance, MRI and MRI targeted biopsies identified an absolute additional 7% of prostate cancer upgrading to TRUS guided biopsy alone. The reviewers concluded that a pre-biopsy MRI should be performed before systematic TRUS-guided biopsies in men on active surveillance, together with MRI-targeted biopsies when indicated to maximize cancer detection.

Similar results were reported in an earlier systematic review, conducted by Radtke et al. in 2015.[28] This review reported that targeted biopsies significantly outperformed conventional systematic biopsies in the detection of significant prostate cancer, which MRI detecting index lesions in approximately 90% of

cases as compared to prostatectomy specimen. The reviewers concluded "in active surveillance, mpMRI avoids underdetection of significant PC and confirms low-risk disease accurately."

Nonrandomized Comparative Studies

Below is a summary of representative studies included in the systematic reviews described above, and addition studies published after these reviews.

In 2015, Walton Diaz et al. published the results of a cohort study that evaluated the performance of mpMRI and MRI-TRUS fusion biopsy for monitoring patients with prostate cancer, including 58 patients undergoing active surveillance.[29] The patients were followed with repeat standard biopsy as well as mpMRI and MRI-TRUS fusion biopsy until there was Gleason score progression (mean of 16 months). Gleason progression was reported in 17 (29%) of men. The PPV and NPV of mpMRI for Gleason progression was 53% (95% CI: 28%-77%) and 80% (95% CI: 65%-91%), respectively. The sensitivity and specificity of mpMRI for increase in Gleason were also 53% and 80%, respectively. The number needed to biopsy to detect Gleason score progression of one grade was 8.74 for standard biopsy versus 2.9 for fusion biopsy (p<0.02).

In 2015, Da Rosa et al. published the results of a prospective cohort study, including 72 patients undergoing active surveillance.[30] The patients were followed for a mean of 38 months. 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 compared with systematic biopsy. Clinically significant cancers were found in seven (37%) identified by MRI-TRUS fusion biopsy and two (11%) by standard systematic biopsy. MRI-TRUS targeted biopsy was 6.3× more likely to yield a core positive for clinically significant cancer compared with standard systematic biopsy (25% versus 4%, p < 0.001). In addition, 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 with systematic biopsy. The NPV of mpMRI for clinically significant cancer was 100%. MRI suspicion level significantly predicted CS cancer on multivariate analysis (OR 3.6, p < 0.001). Overall cancer detection rates were not reported.

In 2016, Recabal et al. reported the results of a series of 206 men who underwent TRUS-alone biopsy and MRI-targeted biopsy. The authors reported that MRI-targeted biopsy failed to detect 17% and 12% of high grade cancers among patients with a moderately suspicious mpMRI result. High grade prostate cancer was detected in all patients with a highly suspicious mpMRI result; however, MRI-targeted biopsy failed to detect the high grade tumor in one (10%) patient. The rate of high grade cancer detection on systematic biopsy was 11% with a negative MRI result. The authors concluded that "MRI-targeted biopsies increased detection of higher grade cancer for men on active surveillance compared to systematic biopsy alone."

In 2017, Frye et al. reported the results of a cohort study of 166 men with low and intermediate risk prostate cancer undergoing active surveillance in whom MRI-visible lesions were monitored by MRI-TRUS fusion biopsy.[31] During a mean follow-up of 25.5 months, MRI-TRUS biopsy identified 22 (44.9%) of 49 patients who progressed compared with systematic biopsy alone, which identified 15 (30.6%) of 49 patients (p=0.03). In other words, fusion biopsy detected 26% more cases of pathological progression on surveillance biopsy compared to systematic 12-core biopsy. In addition, the number of cores needed to

biopsy to detect one pathologic progression was 7.96 (215/27) for systematic biopsy and 3.14 (107/34) for MRI-TRUS biopsy (p<0.001). The authors reported that mpMRI progression in the entire cohort had 81% negative predictive value, 35% positive predictive value, 77.6% sensitivity and 40.5% specificity in detecting pathological progression. The authors concluded that patients with stable mpMRI findings have a low rate of progression and that "incorporating fusion guided biopsy in active surveillance nearly doubled the detection of pathological progression compared to systematic 12-core biopsy."

Noncomparative Studies

Cancer detection rates using MRI-US fusion biopsy for monitoring active surveillance have been reported in 2013 case series. In one series that included 106 men on active surveillance (median PSA 4.1), the detection rate was 63%.[32]

Also in 2013, Bonekamp et al. examined the incremental predictive value of MRI in comparison with clinical parameters for disease reclassification.[33] The authors reported that the PPVs and NPVs for the presence of a suspicious lesion 10 mm or greater predicting disease reclassification were 50% (5/10) and 90% (36/40), respectively. The sensitivity and specificity for the presence of suspicious lesion 10 mm or greater predicting disease reclassification were 56% (5/9) and 88% (36/41), respectively. The presence of multiple suspicious lesions (at least 3 suspicious foci) on MRI predicted disease reclassification with the PPVs and NPVs 100% (4/4) and 89% (41/46), respectively. The sensitivity and specificity for the presence of multiple suspicious lesions predicting disease reclassification were 44% (4/9) and 100% (41/41), respectively. Overall, nine patients were reclassified as not eligible for active surveillance during follow-up. Similar performance measures were also reported in a smaller series of 50 patients also published in 2013.[34]

In 2017, Nassiri et al. examined the ability of MRI-US biopsy to reclassify men undergoing active surveillance, including 259 men with Gleason scores (GS) of 6 (3+3) or 7 (3+4).[35] Overall, pathological upgrading to GS ≥ 4+3 was found in 17/196 men initially presenting with GS 3+3 (8.7%) and 16/63 initially presenting with GS 3+4 (25.4%) (p < 0.01). Of all 33 upgrades, 32 (97%) occurred at an MRI-visible or a tracked site of tumor, rather than at a previously negative systematic site. The authors concluded that "during active surveillance of prostate cancer, targeting of tracked tumor foci by magnetic resonance imaging/ultrasound fusion biopsy allows for heightened detection of Gleason score 4 + 3 or greater cancers."

Evidence Summary

The evidence regarding the use of MRI-TRUS fusion biopsy in the initial biopsy setting leads to improved detection rates of clinically significant cancer has a number of limitations, including significant heterogeneity with regard to patient inclusion criteria, variability in detection calculation methods, lack of blinding, and differences in comparators used between studies. RCTs have published conflicting results as to whether or not the use of MRI-TRUS improved the detection of overall and/or clinically significant cancer. One RCT that reported improved disease detection rates as a result of the use of MRI-TRUS compared to standard systematic TRUS biopsy was not sufficiently powered to detection differences between biopsy techniques and suffered from several limitations, including the fact that the three centers used for the mpMRI had different equipment. While a second more recent multicenter RCT also reported improved disease detection rates using MRI-TRUS, this RCT also suffered from a

number of limitations, including variability in MRI scanners used between centers, variability in operator experience, inclusion of both academic and non-academic centers, and variable use of an endorectal coil. In addition, the systematic reviews published that have assessed the use of MRI-TRUS fusion for initial biopsies have deemed the evidence-base to be of low- to moderate-quality.

Although the body of evidence reporting on the use of MRI-TRUS fusion in the repeat biopsy setting for diagnosis is predominantly comprised of nonrandomized comparative studies, they have consistently reported improved detection of clinically significant cancer when compared to TRUS biopsy alone. Diagnostic MRI-TRUS fusion biopsy consistently detected 18-26% more cases of clinically significant cancer compared to systematic 12-core biopsy in the repeat biopsy setting. While MRI-US fusion biopsy detected 26% more cases of pathological progression in men undergoing active surveillance compared to systematic 12-core biopsies. Furthermore, several studies have reported that the number of cores needed to detect clinically significant cancer upon diagnosis and Gleason score progression is approximately three-fold lower with the use of MRI-TRUS compared to standard TRUS imaging.

The evidence for the use of MRI-TRUS has limitations. However, the use of this fusion imaging modality to support changes in treatment and/or staging for definitive treatment is supported clinically. According to NCCN guidelines, patients who choose to undergo active surveillance are eligible for pelvic ± abdominal MRI with and without contrast for the purposes of staging and characterization of prostate cancer. Results from the MRI may be then used for targeted biopsy when there is a suspicion of cancer progression, as it detects large and poorly differentiated cancers, the presence of extracapsular disease, and possible nodal involvement; all of which may change the course of treatment. In addition, it is clinically appropriate that prior to definitive treatment, MRI results be incorporated into a confirmatory targeted biopsy prior to surgery.

CLINICAL PRACTICE GUIDELINES

National Comprehensive Cancer Network (NCCN)

The current 2022 NCCN prostate cancer early detection guidelines (version 1.2022, updated 2/16/2022) stated the following:[3]

> "The panel believes that the use of multiparametric MRI (MRI) should be considered prior to TRUS-guided biopsy to inform biopsy decisions and to help identify regions of the prostate that may harbor cancer. However, the panel cautions that false negatives can occur and proceeding to TRUS-guided biopsy should still be considered, particularly in situations where the patient is considered to be at high risk for based on PSA density (PSAD) or other biomarkers."[3]

However, the panel's stance on the use of MRI for biopsies differs in the initial and repeat setting.

Initial Biopsy

NCCN authors stated that transrectal or transperineal systematic prostate biopsy under TRUS guidance with or without targeting of lesions seen on pre-biopsy MRI is the recommended technique for prostate biopsy.

Repeat Biopsy

NCCN states that if clinical suspicion of cancer (e.g., those with persistently elevated or rising PSA) persists after a negative biopsy can be considered for MRI followed by a targeted biopsy. NCCN states that that the use of MRI in the repeat biopsy setting has been shown to lead to improved detection of clinically significant disease and to the identification of more low-risk tumors. In addition, the panel stated, "targeted biopsy techniques may help identify regions of cancer missed on prior biopsies and should be strongly considered in patients with a prior negative biopsy and persistent concern for cancer."[3]

NCCN states that if patients have an initial PSA >3ng/ml, a repeat PSA and a DRE, that multiparametric MRI (mpMRI) *may be considered* as an option prior to either TRUS-biopsy OR 6-12-month follow-up.[3]

The current 2022 NCCN prostate cancer treatment guidelines (version 3.2022,) stated the following in the recommendations section of the guidelines:[36]

- Multiparametric MRI (mpMRI) can be used in the staging and characterization of prostate cancer.
- mpMRI may be used to better risk stratify men who are considering active surveillance. Additionally, mpMRI may detect large and poorly differentiated prostate cancer (Grade Group ≥2) and detect extracapsular extension (T staging).

American Urological Association (AUA)

In 2018, the AUA published a policy statement addressing standard operating procedure for MRI of the prostate. The statement concluded that data was "insufficient…to recommend routine MRI in every biopsy naïve patient under consideration for prostate biopsy," but noted that "its use may be considered in men for whom clinical indications for biopsy are uncertain (minimal PSA increase, abnormal DRE [digital rectal examination] with normal PSA [prostate specific antigen], or very young or old patients)."[37]

American Urological Association (AUA)/ Society of Abdominal Radiology (SAR)

In 2016, the AUA/SAR published a consensus statement addressing MRI-TRUS in patients with a prior negative biopsy.[38] Following a non-systematic literature review, the expert panel concluded the following:

- Patients [with prior negative biopsy] receiving a PI-RADS [Prostate Imaging-Reporting and Data System] assessment category of 3 to 5 warrant repeat biopsy with image guided targeting.
- While transrectal ultrasound guided magnetic resonance imaging fusion or in-bore magnetic resonance imaging targeting may be valuable for more reliable targeting, especially for lesions that are small or in difficult locations, in the absence of such targeting technologies cognitive (visual) targeting remains a reasonable approach in skilled hands.
- Given the number of studies showing a proportion of missed clinically significant cancers by magnetic resonance imaging targeted cores, a case specific decision must be made whether to also perform concurrent systematic sampling.[38]

American College of Radiology (ACR)

The 2016, the ACR updated their Appropriateness Criteria® for Prostate Cancer–Pretreatment Detection, Surveillance, and Staging. Imaging technologies a rating of 7, 8, or 9 are considered to be "usually appropriate."[6]

For detection in patients with clinically suspected prostate cancer and no prior biopsy, TRUS-guided biopsy was rated as a "9", and MRI targeted biopsy was given a "7". The ACR guideline stated "MRI in biopsy naïve patients *may be performed before TRUS-guided biopsy so the targeted sample may be obtained using MRI or TRUS fusion technology in patients with appropriate targets*. MRI is complementary to TRUS-guided biopsy in this setting."

For detection in patients with a prior negative TRUS-guided biopsy, AND in patients undergoing active surveillance, the ACR rated MRI targeted biopsy as an "8" and TRUS as a "7", stating that when repeating a TRUS-guided biopsy in these patients "MRI should be performed first so that MRI-targeted biopsies (fusion or in-bore technique) can be obtained from appropriate suspicious lesions."

The 2017, the ACR updated their Appropriateness Criteria® for Prostate Cancer–Posttreatment Detection, Surveillance, and Staging.[5]

For prostate cancer follow-up in patients whose have undergone nonsurgical local and pelvic treatments and there is clinical concern for residual or recurrent disease, both MRI-targeted biopsy and TRUS guided biopsy were considered "usually appropriate" (no number ratings were provided).

CENTERS FOR MEDICARE & MEDICAID

As of 3/16/2022, no specific Medicare coverage policy or guidance (e.g., manual, national coverage determination [NCD], local coverage determination [LCD] article [LCA], etc.) was identified which addresses MRI-TRUS fusion biopsy as a modality for the diagnosis and management of prostate cancer. In the absence of a NCD, LCD, or other Medicare policy, Medicare guidelines allow a Medicare Advantage Organization (MAO) to make coverage determinations, applying an objective, evidence-based process, based on authoritative evidence. (Medicare Managed Care Manual, Ch. 4, §90.5) Therefore, this Company coverage review will be applied for medical necessity decision-making.

Under Medicare, only medically reasonable and necessary services are covered (Title XVIII of the Social Security Act, §1862(a)(1)(A)). Procedures, devices, or other medical technologies which lack scientific evidence regarding safety and efficacy because they are investigational or experimental are considered "not medically reasonable or necessary" for Medicare Plan members. (Medicare Claims Processing Manual, Ch. 23, §30 A).

POLICY SUMMARY

Diagnostic Biopsies

There is sufficient evidence that the use of MRI-TRUS fusion imaging for targeted biopsies leads to a higher rate of detection and diagnosis of clinically significant cancer in the repeat biopsy setting. In addition, the current NCCN guidelines recommend the use of targeted biopsy techniques, including MRI-TRUS fusion, in this clinical setting.

The evidence for the use of MRI-TRUS fusion biopsy in the initial biopsy setting cancer has considerable limitations. These limitations include significant heterogeneity in patient inclusion criteria between studies, MRI machines used within and between studies, heterogeneity in detection rate calculations, lack of blinding, and different comparator groups. The most recent NCCN guidelines indicate that in the setting of initial biopsy, MRI-guided targeted biopsies "can be considered…in those centers with MRI availability and with experience and expertise in MRI interpretation and targeting" but noted that "considerable interreader variability exists…[and] more information is needed about the generalizability of findings…" NCCN states that the use of MRI has not conclusively been shown to reduce the number of men undergoing biopsy, reduce the detection of indolent disease, or improve detection of clinically significant disease in the setting of initial biopsy.

Active Surveillance

The evidence for the use of MRI-TRUS has limitations when used in the setting of active surveillance. However, the use of this fusion imaging modality to support changes in treatment and/or staging for definitive treatment is supported clinically. According to NCCN guidelines, patients who choose to undergo active surveillance are eligible for pelvic ± abdominal MRI with and without contrast for the purposes of staging and characterization of prostate cancer. Results from the MRI may be then used for targeted biopsy when there is a suspicion of cancer progression, as it detects large and poorly differentiated cancers, the presence of extracapsular disease, and possible nodal involvement; all of

which may change the course of treatment. In addition, it is clinically appropriate that prior to definitive treatment, MRI results be incorporated into a confirmatory targeted biopsy prior to surgery.

INSTRUCTIONS FOR USE

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days' notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

REGULATORY STATUS

Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

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