Anthem

Clinical UM Guideline

Subject: Prostate Biopsy using MRI Fusion Techniques
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Description

This document addresses prostate biopsies using a fusion technique in which multiparametric magnetic resonance imaging (mpMRI) is fused with real-time high definition prostate ultrasound images through the use of specialized equipment and software. This enables the ability to target and biopsy areas suspicious for prostate cancer.

Note: Please see the following related documents for additional information:

- CG-MED-45 Transrectal Ultrasonography
- SURG.00107 Prostate Saturation Biopsy

Clinical Indications

Medically Necessary:

The use of multiparametric magnetic resonance imaging fusion with rectal ultrasound for targeted biopsy of the prostate is considered **medically necessary** for individuals with:

- A persistently elevated or rising prostate specific antigen; **and**
- An mpMRI with at least one lesion reported on a Likert scale equal to or greater than 3, or scored equal to or greater than 3 according to the Prostate Imaging Reporting and Data System (PI-RADS) scoring system.

Not Medically Necessary:

The use of multiparametric magnetic resonance imaging fusion with rectal ultrasound for targeted biopsy of the prostate is considered **not medically necessary** when the above criteria are not met and for all other indications.

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

CPT	
55899	Unlisted procedure, male genital system [when specified as MRI-fusion targeted biopsy of the prostate] **Note:** there is no specific code for MRI-fusion targeted biopsy of the prostate; if CPT codes 76942 plus a prostate biopsy code such as 55700 are used to describe this procedure, the medically necessary criteria will be applied

ICD-10 Diagnosis	
C61	Malignant neoplasm of prostate
D07.5	Carcinoma in situ of prostate
D29.1	Benign neoplasm of prostate
D40.0	Neoplasm of uncertain behavior of prostate
R97.2	Elevated prostate specific antigen [PSA]
Z12.5	Encounter for screening for malignant neoplasm of prostate
Z85.46	Personal history of malignant neoplasm of prostate

When services are Not Medically Necessary:
For the procedure codes listed above when criteria are not met or for situations designated in the Clinical Indications section as not medically necessary.

Discussion/General Information

Prostate cancer is the most common diagnosed cancer, other than skin cancers, in North American men (individuals born with a prostate). The American Cancer Society notes that in 2022 there were an estimated 268,490 new cases of prostate cancer and about 34,500 disease-related deaths in the United States. Prostate cancer is the second leading cause of cancer death in American men (individuals born with a prostate), exceeded only by lung cancer. Persons in the United States have about 1 chance in 8 of eventually being diagnosed with this malignancy and about 1 person in 41 will eventually die of the disease (American Cancer Society, 2022).

The standard approach for the detection of prostate cancer has traditionally been an ultrasound-guided biopsy via transrectal ultrasound (transrectal ultrasound guided biopsy). Additional technology is now being studied and used for assistance in the diagnosis of prostate cancer. One such approach is the use of multi-parametric magnetic resonance imaging (mpMRI). This technology involves a modification to MRI which selectively combines T2-weighted MRI features (for anatomical imaging) with dynamic contrast enhanced (DCE) and diffusion weighted imaging (DWI) for detailed visualization and characterization. The mpMRI, combined with ultrasound imaging, can be used to create a three-dimensional view of the prostate. This allows for targeted biopsies, which have been proposed to improve prostate biopsy precision. The United States Food and Drug Administration (FDA) has cleared several of these devices through their 510(k) premarket process.

In a 2014 study by Siddiqui and colleagues, the authors sought to determine if a standard biopsy was necessary if the targeted-MRI approach was also done. All participants in this study (n=1215) underwent mpMRI and subsequently mpMRI/ultrasound fusion biopsy and standard biopsy. A total of 181 participants did not have lesions, leaving 1034 to proceed with biopsy. After additional exclusions, 1003 participants were included in the study. The targeted mpMRI/ultrasound fusion-directed biopsies diagnosed 461 cases of prostate cancer and the standard, systematic approach to biopsy diagnosed 469 cases of prostate cancer with exact agreement between approaches for 690 subjects (69%). When the standard biopsy cores were combined with the targeted mpMRI approach, an additional 103 cases of prostate cancer were diagnosed (of which 83% were considered low risk, 12% were intermediate risk, and 5% were high risk). The predictive ability of targeted biopsy for differentiating low-risk from intermediate- and high-risk disease in 170 subjects with whole-gland pathology after prostatectomy was greater than that of standard biopsy or the two approaches combined (area under the curve, 0.73, 0.59, and 0.67, respectively; $p<0.05$ for all comparisons). The authors noted that mpMRI/ultrasound fusion was associated with increased detection of high-risk prostate cancer and decreased detection of low-risk prostate cancer, but that additional study would be needed to determine clinical impact, such as recurrence of disease and prostate cancer-specific mortality.

A 2015 study by Kim and colleagues compared targeted mpMRI prostate biopsies to conventional transrectal ultrasound guided biopsies. A total of 34 subjects received targeted mpMRI biopsy and were individually matched to 34 subjects who received conventional biopsy. Findings were correlated to Gleason Scores to determine clinical significance. As compared with the conventional ultrasound, mpMRI imaging suspicious biopsies had a significantly higher overall prostate cancer detection (54% vs. 24%, $p<0.01$) and Gleason score ≥ 7 detection (25% vs. 8%, $p<0.01$). When compared with conventional ultrasound, mpMRI had similar detection rates for benign prostate tissue (76% vs. 79%, $p=0.64$), and Gleason score ≤ 6 (16% vs. 14%, $p=0.49$), and Gleason score ≥ 7 detection (8% vs. 7%, $p=1.0$).

Da Rosa (2015) compared mpMRI-targeted fusion biopsy to transrectal ultrasound-guided biopsy in 72 subjects with prostate cancer in active surveillance with rising prostate specific antigen (PSA) or an appropriate rebiopsy interval. A total of 19 participants were found to have clinically significant prostate cancer (Gleason score greater than 7): 7 with mpMRI-targeted fusion biopsy alone, 2 by transrectal biopsy and 10 cases by both ($p=0.182$). The authors concluded that the mpMRI-targeted fusion biopsy resulted in detection of 7 additional cancers (37% of 19 cases). The proportion of cores positive for Gleason score 7 was 6.3 times higher with mpMRI-targeted fusion biopsy compared with transrectal ultrasound-guided (25% of 141 targeted cores versus 4% of 874 systematic cores, $p<0.001$). Using the Gleason > 6 threshold, 31/72 participants had clinically significant cancer, 10 identified by mpMRI-targeted fusion biopsy alone, 5 by transrectal ultrasound-guided biopsy alone, and 16 by both methods ($p=0.302$). The proportion of cores positive for clinically significant cancer was 6.2 times higher with mpMRI-targeted fusion biopsy compared with transrectal ultrasound-guided (37% of 141 targeted cores versus 6% of 874 systematic cores, $p<0.001$). For the 37 individuals with an mpMRI score ≥ 4, the authors calculated a positive predictive value for cancer as 49% if they had Gleason score ≥ 7 and positive predictive value at 78% if they had Gleason score equal to 6 with > 50% involvement in any core. Negative predictive value for the presence of any cancer was 44%. The authors note that “there is a trend toward” detecting more clinically significant cancers.

Lee and colleagues (2016) compared diagnostic outcomes between two different techniques for targeting regions-of-interest on mpMRI; MRI-ultrasound fusion (MR-F) and ultrasound guided visually targeted (VT) biopsy. The primary endpoint was the difference in the detection of high-grade (Gleason ≥ 7) and any-grade cancer between VT and MR-F. Secondary endpoints were the difference in detection rate by biopsy location using a logistic regression model, and difference in median cancer length. The authors identified 396 regions-of-interest in 286 subjects. The difference in high-grade cancer detection between MR-F biopsy and VT biopsy was -1.4% (95% confidence interval [CI], -6.4% to 3.6%; $p=0.6$); for any-grade cancer the difference was 3.5% (95% CI, -1.9% to 8.9%; $p=0.2$). Median cancer length detected by MR-F and VT were 5.5 mm vs. 5.8 mm, respectively ($p=0.8$). MR-F biopsy detected 15% more cancers in the transition zone ($p=0.046$), and VT biopsy detected 11% more high-grade cancer at the prostate base ($p=0.005$). Only 52% of all high-grade cancers were detected by both techniques. The authors concluded that there was insufficient evidence to support a difference in the detection of high-grade or any-grade cancer between VT and MR-F biopsy. However, the performance of each technique varied in specific biopsy locations, and the outcomes of both techniques were complementary. The authors suggest that combining VT biopsy and MR-F biopsy may optimize prostate cancer detection.

A retrospective review by Oberlin and colleagues (2016) reported on 231 subjects who underwent mpMRI-targeted biopsy; 81 individuals had fusion biopsy and 151 individuals had cognitive biopsy of the prostate. All eligible individuals in the study had an abnormal screening test with an elevated PSA or abnormal digital rectal exam, and active surveillance of prostate cancer. The primary outcome was the overall detection rate of cancer and the secondary outcome was the detection of clinically significant cancer. In the fusion group, 48.1% of the individuals had cancer detected compared to 34.6% in the cognitive group. When the mpMRI fusion group was compared to the conventional transrectal ultrasound biopsy group, the MRI group detected 61.5% of Gleason grade 7-10 cancer compared to 37.5% in the ultrasound group.

In a 2016 retrospective analysis of prospectively generated clinical, imaging and pathologic data, Mariotti and colleagues studied the performance of systematic vs. targeted biopsies in general clinical practice, and reported on 389 subjects who had mpMRI of the prostate followed by systematic and then MRI-targeted transrectal ultrasound fusion guided biopsy. Targeted biopsies were performed using different fusion systems and a heterogenous group of radiologists and urologists using differing protocols on differing patient populations. Individuals with a previous diagnosis of prostate cancer were excluded. Suspected prostate cancer was diagnosed in 202/389 subjects using the systematic approach, 182/389 subjects using the targeted approach, and 235/389 subjects had prostate cancer diagnosed using the combined targeted and systematic approach. The targeted biopsy diagnosed 11% more intermediate- to high-risk tumors when compared to the systematic biopsy ($p<0.0001$) and 16% fewer low-risk tumors ($p<0.0001$). The results were replicated when data from subjects who were biopsy-naïve and those who had previous negative biopsies were analyzed.

Hansen and colleagues (2016) reported on transperineal biopsy and mpMRI and transrectal ultrasound fusion imaging for 534 individuals with Gleason score ≤ 6: 107 had no previous prostate biopsy, 295 had a prior benign transrectal-guided biopsy, and 159 were on active surveillance for low-risk cancer. A total of 378 participants had Likert 3-5 MRI lesions reported, cancer was detected in 249 participants, and 157 participants had a new Gleason score 7-10 cancer. Gleason 7-10 cancer was detected in 45% of individuals on active surveillance for low-risk cancer, 27% in individuals with a previous benign biopsy, and 39% in individuals with no previous biopsy. The positive predictive value for detecting Gleason 7-10 was: for Likert 3, 0.15; for Likert 4, 0.43 and for Likert 5, 0.63. The negative predictive value of predicting Likert 1-2 findings was 0.60 for excluding any cancer, 0.87 for excluding Gleason 7-10 and 0.97 for excluding Gleason ≥ 4+3. The authors further note that “Not all men with moderately elevated PSA values and an unsuspicious prostate mpMRI read by experienced radiologists need prostate biopsies.”

In a 2017 study by Hoffman and colleagues, 99 subjects with elevated PSA, at least one prior negative standard core biopsy and no previous pretreatment of prostate cancer underwent mpMRI followed by ultrasound-fusion-guided perineal biopsy. MpMRI results indicated that 6 participants had presumed benign disease, 21 participants had ambiguous diagnostic findings, and 72 participants displayed PIRADS/PR scores suggestive of malignancy. A total of 33 participants did not show any signs of malignancy upon histopathological exam following fusion guided targeted biopsy while the remaining 66 participants had prostate cancer diagnosed in the suspicious regions. Only 2 subjects had cancer diagnosed through random biopsy. The overall sensitivity for mpMRI to differentiate between low- and high-grade lesion differentiation (GS less than or equal to 7a vs. greater than or equal to 7b) via PR

was 88%, with a negative predictive value of 70% (p=0.74; Fisher's exact test). While this was a relatively small group of participants at a single center, the mpMRI followed by ultrasound fusion biopsy showed higher detection rates of prostate malignancy than conventional diagnostic procedures.

A 2017 study by Simmons and colleagues reported on the diagnostic accuracy of mpMRI in participants requiring a repeat prostate biopsy at an expert referral center. A total of 249 participants had previous transrectal ultrasound biopsy and were advised to undergo further biopsies. All 249 participants then underwent mpMRI. Radiologists were blinded to the initial biopsies. Using Likert score greater than or equal to 3, a total of 214 participants had a positive prostate mpMRI. When correlated to biopsy findings, this yielded a sensitivity of 97.1% (95% CI: 92-99), specificity of 21.9% (15.5-29.5), NPV 91.4% (76.9-98.1), and PPV 46.7% (35.2-47.8). When a Likert score greater than or equal to 4 was used, a total of 129 participants had a positive mpMRI, yielding a sensitivity of 80.6% (71.6-87.7), specificity of 68.5% (60.3-75.9), negative predictive value (NPV) 83.3% (75.4-89.5), and positive predictive value (PPV) 64.3% (55.4-72.6). The authors cautioned that insignificant cancers can be detected when an mpMRI threshold score of 3 is used to designate suspicious mpMRI, noting as well that among other published studies wide ranges are used in mpMRI protocols, study populations, reference standards, and mpMRI reporting.

In a 2018 study by Kasivisvanathan and colleagues, 500 participants were randomized to either mpMRI targeted biopsy (n=252) or standard biopsy (n=248). Of the participants in the mpMRI targeted group, 71 had MRI results that were not indicative of prostate cancer and did not have biopsy, compared to 235 participants in the standard biopsy group. A total of 95 participants (39%) in the mpMRI group were found to have clinically significant prostate cancer and 23 (9%) with insignificant cancers, compared to 64 participants (27%) in the standard biopsy group with 55 (22%) insignificant cancers. Using MRI-targeted biopsy, 78 (31%) of participants were able to avoid biopsy and fewer subjects in the MRI-targeted biopsy group than in the standard biopsy group received a diagnosis of clinically significant cancer (adjusted difference, -13 percentage points, 95% CI, -19 to -7; p<0.001). The authors conclude that the use of risk assessment with MRI before biopsy and MRI-targeted biopsy was superior to standard transrectal ultrasonography-guided biopsy in subjects at clinical risk for prostate cancer who had not undergone biopsy previously. However, the authors caution that there is room for improvement in attaining consistency in reporting the results of mpMRI and further research is necessary regarding standardization and reproducibility.

A 2018 study by Tomašković and colleagues reported on whether the application of magnetic resonance–ultrasound (MR-US) fusion biopsy resulted in improved detection of prostate cancer compared to repeat conventional biopsy (control group) in individuals with previous negative systematic transrectal ultrasound (TRUS)-guided biopsy and persistently elevated or rising PSA levels. A total of 101 subjects were included in this prospective study. Twenty-four (24) subjects had previous mpMRI, followed by cognitive fusion biopsy of the prostate with 8-10 systematic biopsy cores and 1-3 targeted biopsy cores according to mpMRI findings. Seventy-seven (77) subjects underwent only a classic, repeated TRUS biopsy without prior image processing. Lesions were classified according to the PI-RADS system. Cancer detection rate according to PIRADS-v2 in subjects with detected lesion on mpMRI was: PIRADS 1, n=0; PIRADS 2, n=0; PIRADS 3, n=0; PIRADS 4, n=6/8 (75%); and PIRADS 5, n=2/3 (67%). In the group of subjects who underwent MR-TRUS cognitive fusion biopsy, the prostate cancer detection rate was 8/24 (33%) and in the control group the detection rate was 12/77 (16%). There are limitations to this study including that referrals for mpMRI were done according to their physician preferences and biopsies were performed by one urologist and all MRIs were interpreted by an experienced uroradiologist. The authors caution that less experienced urologists and radiologists might not achieve the same diagnostic yield. Taking into account the operator dependent reading and interpretation, as well as diagnostic accuracy of biopsy itself, when there is a prior negative biopsy with persistent suspicion of prostate cancer, the lesions found on mpMRI are better visualized which allows for better sampling.

In a 2019 three-armed multicenter randomised controlled trial by Wegelin and colleagues, the authors compared the overall prostate cancer and clinically significant prostate cancer detection rates of three MRI targeted biopsy techniques and sought to identify whether there was a superior technique regarding diagnostic efficacy in a repeat biopsy setting. Included were 665 subjects with prior negative systematic biopsy and a persistent suspicion of prostate cancer. All participants underwent 3-T mpMRI evaluated with PIRADS version 2. The participants with imaging showing PIRADS greater than or equal to 3 lesions (n=234), were randomized to one of three MRI targeted biopsy techniques; MRI-transrectal ultrasound fusion (n=79), cognitive registration (n=78), or in-bore MRI (n=77). There were 115 prostate cancers and 78 clinically significant prostate cancers detected using targeted biopsy. None of the three groups showed a significant difference in the detection rates of overall prostate cancer (MRI-transrectal ultrasound fusion 49.4%, cognitive registration 43.6%, and in-bore MRI 54.5%) or in the detection of clinically significant prostate cancer (transrectal ultrasound fusion 34.2%, cognitive registration 33.3%, and in-bore MRI 32.5%). One study limitation is the relatively low number of participants with PIRADS greater than or equal to 3 lesions on mpMRI leading to underpowering for the primary endpoint. Also to note is the lack of a consensus on the definition of clinically significant prostate cancer. Generalizability may not be possible since there was an expert team of urologists and radiologists involved in this study regarding prostate cancer diagnosis. For those individuals with a prior negative prostate biopsy and persistent suspicion of prostate cancer, the rate of cancer suspicious regions on mpMRI was 35%. If targeted biopsy of these regions is done, the detection rate would be 49% for prostate cancer and 33% for clinically significant prostate cancer.

In a 2019 retrospective review of charts by Lo and colleagues, the primary objective was to estimate the negative predictive value of mpMRI in detecting clinically significant prostate cancer for individuals with an elevated PSA or abnormal digital rectal exam but a negative preMRI transrectal ultrasound guided biopsy. A secondary objective was to estimate the overall negative predictive value, positive predictive value, sensitivity and specificity of mpMRI for detecting clinically significant prostate cancer at an intermediate to long-term follow-up. There were 121 mpMRI scans done in subjects with a prior negative systemic biopsy. The median PSA was 9.5 ng/dl. With a median follow-up of 6.7 years, subjects with negative mpMRI remained free of clinically significant prostate cancer. Overall negative predictive value of mpMRI was 86%, positive predictive value was 54%, sensitivity was 92%, specificity was 40% with a prevalence of clinically significant prostate cancer of 44%. The study has several limitations including its retrospective design, differing imaging intervals and MRI protocols, and the inability to correlate a positive biopsy with the same lesion found on MRI. The scans in this study were done prior to the advent of the PI-RADS v2 scoring system. A prospective cohort should be used to verify the ability of mpMRI in evaluating negative predictive value in a clinical setting.

In a 2020 retrospective review by Fujii and colleagues, the authors reported on 131 biopsy-naïve Japanese subjects with an elevated serum PSA to assess the benefits of mpMRI/TRUS targeted fusion biopsy. Prior to biopsy, mpMRI and real-time TRUS images were obtained and then fused together. Targeted biopsy was done first followed by 10-core standard biopsy. The overall cancer detection rate was 61.1% in both standard biopsy and targeted biopsy. Clinically significant prostate cancer was detected in 57 participants (43.5%) by targeted biopsy versus 47 participants (35.9%) by standard biopsy. Clinically insignificant prostate cancer was detected in 23 participants (17.6&) by targeted biopsy versus 33 participants (25.2%) by standard biopsy. There were 1310 cores collected by standard biopsy and 489 cores collected by targeted biopsy. The overall cancer detection rate was 42.3% for the targeted biopsy cores versus 17.9% for the standard biopsy cores. While this study has limitations including the retrospective and single facility design, there was an improvement in the detection of clinically significant prostate cancer and reduction of clinically insignificant prostate cancer by targeted biopsy compared to standard biopsy.

A 2021 multicenter randomized controlled study by Izadpanahi and colleagues reported on the diagnostic yield of fusion MRI-guided targeted biopsy in combination with systematic biopsy to cognitive (visual) targeted biopsy in combination with systematic biopsy.

Participants included 199 biopsy-naïve subjects with either increased PSA levels or abnormal digital rectal exam. All participants underwent mpMRI and those with suspicious lesions and PI-RADS score of 3 or greater were randomized to either fusion MRI-guided targeted biopsy with systematic biopsy (n=99) or cognitive targeted biopsy with systematic biopsy (n=100). In the fusion group, the average number of positive scores was 0.13 ± 0.05 compared to 0.08 ± in the cognitive group. The overall cancer detection rate in the fusion group was 44.4% versus 31.0% in the cognitive group. Detection of clinically significant prostate cancer in the fusion group was 33.3% compared to 19.0% in the cognitive group. In this study, participants had PSA levels between 2 and 10 ng/dL which may limit generalizability among other populations.

In a 2020 prospective, single-arm study by Amin and colleagues, the authors reported on the diagnostic utility of baseline and serial mpMRI to predict biopsy proven progression to clinically significant prostate cancer in those on active surveillance and assessed the safety of active surveillance in which an mpMRI replaces confirmatory biopsy at 1 year (using abnormalities found on mpMRI to trigger a prostate biopsy). This study defined MRI progression as any new PI-RADS 3 lesion or persistent PI-RADS 4/5 lesion. There were 172 subjects enrolled. This study reports on the 3-year results of the first 100 subjects who completed the study. Inclusion criteria were those with histologically proven prostate cancer as evidenced by Gleason 3+3 = 6 or Gleason 3+4 = 7 with 10% or less Gleason pattern 4 overall and less than 2 cores Gleason pattern 4. Baseline median PSA was 4.7 ng/ml. At the end of the study, clinically significant prostate cancer was noted in 8/71 subjects with negative surveillance mpMRI and 13/29 subjects with a positive surveillance mpMRI. Sensitivity was reported as 61%, specificity 80%, positive predictive value 45%, and negative predictive value 89%. Of the 8 participants with clinically significant prostate cancer not confirmed by mpMRI, none of them had a prostate specific antigen density greater than 0.2 ng/ml. At final biopsy, the subjects with prostate specific antigen density greater than 0.2 ng/ml had positive predictive value 50% with negative predictive value 83%. There were 20 subjects who underwent radical prostatectomy at the end of the study. Pathological progression was found in 17/20 (with 3 subjects having radical prostatectomy based on personal preference). There were no significant differences in median tumor volume, pathological T stage, or rates of positive surgical margins in those with or without a positive lesion on mpMRI. The authors note that additional research will need to be done define what constitutes a change in lesion and that while confirmatory biopsy can be avoided in the majority of those on active surveillance, they do not recommend surveillance biopsies be entirely replaced by mpMRI as there are a small number of significant high-grade tumors which are missed by mpMRI.

A 2020 study by Ahdoot and colleagues reported on subjects with MRI-visible prostate lesions who underwent both MRI-targeted fusion biopsy and systematic biopsy to determine the most effective method for diagnosis of prostate cancer according to grade group. In this study, grade group 1 (Gleason score 3+3=6) was defined as clinically insignificant disease. Grade group 2 was defined as Gleason score, 3+4=7; favorable intermediate risk. Grade group 3 (Gleason score, 4+3=7; unfavorable intermediate risk) or higher was defined as clinically significant cancer. Primary outcome was the cancer detection rate according to grade group for each biopsy method. Inclusion criteria was adult individuals with an elevated PSA or abnormal DRE. Participants were excluded if they had previous treatment for prostate cancer, no visible lesions on MRI, or inability to have MRI. There were 2732 participants who had prostate MRI. Of those, 2180 had visible lesions on MRI and then had combined MRI-targeted and systematic biopsies. After excluding 77 participants since they had previous prostate cancer treatment, 2103 participants were included in the analysis. Prostate cancer was diagnosed in 1104 participants by systematic biopsy alone and 1084 participants by MRI-targeted biopsy alone. The MRI-targeted biopsy showed more diagnoses of cancers in grade groups 3, 4, and 5 than systematic biopsy. MRI-targeted biopsy also showed fewer cancers in grade group 1. When MRI-targeted biopsies were done in addition to systematic biopsies, there were 208 more prostate cancer diagnoses, 59 of which were considered clinically significant (grade group ≥3). There were 134 participants initially diagnosed with grade group 1 cancer following systematic biopsy and were upgraded to grade group 2 or higher when targeted MRI was added. Additionally, following MRI-targeted biopsy, 74 participants who had no cancer detected on systematic biopsy were diagnosed with grade group 1 cancer. Generalizability may be limited as this was a single-center study with practitioners experienced in performing and interpreting MRI and histopathological analysis. The study also focused only on those individuals with lesion visible on MRI.

Klotz and colleagues (2021) reported on a phase 3 multicenter, randomized, noninferiority trial to ascertain whether mpMRI with only targeted biopsy was noninferior to systematic TRUS biopsies in the detection of prostate cancer. Primary outcome was the proportion of participants with clinically significant prostate cancer defined by International Society of Urological Pathology grade group (GG) 2 or greater. Secondary outcomes were those who had clinically significant prostate cancer (GG1), GG3 or greater prostate cancer, no significant cancer but positive mpMRI results and/or GG2 or greater cancer found on repeated biopsy by 2 years. There were 453 participants enrolled with 226 in the TRUS biopsy arm and 227 in the mpMRI arm. In the TRUS biopsy arm, 24 participants left the study before the first intervention and 6 participants in the mpMRI arm left the study before the mpMRI. Of the participants in the mpMRI arm, 138/221 had positive results (defined as PI-RADS score greater than or equal to 3). Negative mpMRI results were found on 83/221 participants and therefore avoided biopsy. After biopsy, 79 participants in the mpMRI arm and 67 participants in the TRUS biopsy arm had GG2 or greater cancer detected. The mpMRI arm showed fewer diagnoses of GG1 prostate cancer (n=23) compared to TRUS biopsy (n=49). There were 30 participants in the mpMRI arm and 25 participants in the TRUS biopsy arm who had GG3 or greater cancer detected. Of the participants who underwent biopsy, GG2 or greater prostate cancer was found in 79 by mpMRI and 67 by TRUS biopsy. Generalizability may be limited as MRI interpretation and biopsies were done by experienced radiologists and urologists.

Doan and colleagues (2022) reported a single-arm, non-blinded, prospective trial over 5 years of 172 men (individuals born with prostates). Five individuals were excluded due to not meeting inclusion criteria or withdrawing from the study, 10 were excluded due to protocol breaches or lost to follow up, and 9 individuals refused the end of protocol biopsy (n=148). The primary outcome measured was clinically significant prostate cancer captured during the protocol period and the rate of progression to treatment. Individuals identified with prostate cancer had Gleason 3+3=6, or Gleason 3+4= 7 with 10% or less Gleason pattern 4 overall, and <2 cores Gleason pattern 4. Baseline mpMRI and targeted biopsy were performed, then repeat mpMRI imaging at years 1 and 2, with a biopsy at the end of year 3. Biopsies during the 3-year period were initiated by abnormalities on mpMRI. Additionally, PSA was performed every 6 months and DRE yearly. A PSA density >0.2 ng/ml/cc or abnormal DRE also initiated consultation with the treating urologist to assess the need for early biopsy. During the study there were no guidelines yet published that clearly defined “MRI progression” in serial mpMRI. An expert consensus determined this should be defined as: persistent Prostate Imaging Reporting and Data System (PI-RADS) 4/5 lesion (even if previously reported as 4/5), or new PI-RADS 3 lesions (increased from PI-RADS 1-2 previously). The 3-year end of protocol biopsy was performed transperineally with a targeted template approach, which included a median of 33 cores (Q1-Q3 28-37), and a minimum of 18 cores from 14 regions. Individuals with negative serial mpMRI 14% (15/108) had clinically significant prostate cancer compared to 50% (20/40) with a positive serial mpMRI. The results demonstrated that sensitivity was 57%, specificity 82%, positive predictive value 50% (mpMRI 6.20, p< 0.001 and PSA 6.19, p=0.001), negative predictive value was 86 %. Four individuals 2.3 %, (4/172) had false-negative mpMRI. At the end of the 3 years, 24% (n=35/148) of individuals developed pathological progression. The study limitations included single-arm design, lack of precise criteria for MRI progression and the use of saturation template biopsy. The authors concluded that mpMRI and PSA density were predictors of progression and thus could reduce frequency of biopsy and increase compliance with active surveillance, and that standardized 3-year systematic biopsy remains necessary due to possible MRI-invisible tumors.

In 2022 Exterkate and colleagues published a sub-analysis of 665 individuals from the previously discussed FUTURE trial. The study

was a prospective, multicenter, randomized controlled trial (RCT) of individuals with prior negative biopsy, despite persistent elevated PSA, and/or suspicious DRE. The study assessed the proportion of prostate cancer found in individuals with negative biopsy and non-suspicious mpMRI during follow up. The primary outcome measured was the number of clinically significant prostate cancer cases (Gleason ≥3 + 4/International Society of Urological Pathology grade group ≥2) identified during follow-up compared to the expected incidence in the general population. In total, 65% of participants (431/665) had a non-suspicious mpMRI, the initial median serum PSA level was 8.1 ng/mL, the median prostate volume was 58 ng/mL, and the median PSA density was 0.11 ng/mL. At the median interval of 33 months, a total of 38/431 individuals (8.8%) were diagnosed with prostate cancer, of whom 13 (3.0%) were diagnosed with clinically significant prostate cancer, and 25 (5.8%) were diagnosed with clinically non-significant prostate cancer. Clinically significant prostate cancer was identified after a median follow-up of 44 months compared to clinically non-significant prostate cancer after a median 27 months (p=0.16). The standardized incidence ratio analysis for clinically significant prostate cancer was 4.3 % (95% confidence interval 2.3–7.4; total excess of eight cases).The authors concluded that after a negative prior biopsy and non-suspicious mpMRI, the risk of clinically significant prostate cancer in individuals with elevated PSA and/or suspicious DRE is low. However, compared to the general population, the risk remains increased despite the high negative predictive value of mpMRI. The study limits included short length of follow up, and a cohort who was already under surveillance, therefore comparisons to the general population are inconclusive. Additional research is needed on risk-adapted surveillance strategies.

Grey and colleagues (2022) reported a prospective, multicentre, paired-cohort, study of 306 individuals that examined the consistency between mpMRI and multiparametric ultrasound to detect clinically significant prostate cancer. Individuals at risk of prostate cancer, aged 18 years or older, with elevated PSA and abnormal findings on DRE underwent both multiparametric ultrasound and mpMRI. Individuals with positive findings on either imaging study then had targeted biopsies but were masked to the results. The primary outcomes measured were the number of positive lesions found, and agreement between mpMRI and multiparametric ultrasound in identifying them (Likert score of ≥3), and the detection of clinically significant cancer (defined as a Gleason score of ≥4+3 in any area or a maximum cancer core length of ≥6 mm of any grade [PROMIS definition 1]), in individuals who had a subsequent biopsy. The results demonstrated that multiparametric ultrasound was positive in 272/306 (89%) of individuals and mpMRI was positive in 238/306 (78%) individuals. Positive test agreement was 73.2%. Combining both tests detected 83/257 (32%) of clinically significant cancer, of these 6/83 (7%) were detected exclusively with multiparametric ultrasound, and 17/83 (20%) were exclusively detected by mpMRI (agreement 91.1%). No p values were reported. No adverse events were reported. The authors concluded that multiparametric ultrasound detected 4.3% fewer clinically significant prostate cancers than mpMRI, however it led to 11.1% more individuals being referred for biopsy. Both imaging tests missed clinically significant cancers detected by the other. The use of both tests may increase detection compared with using each test independently.

Porpiglia and colleagues (2023) published a single center, prospective, non-inferiority, parallel two armed, RCT of 397 individuals with suspicion of prostate cancer, positive mpMRI, and whom had no prior biopsy. Individuals included in the study were aged < 75 years old, biopsy naïve, with serum PSA <15 ng/ml, and positive mpMRI (defined as presence of Pi-Rads v.2>3 lesion, as determined by EAU Guidelines). Individuals were randomly assigned to Arm A (fusion biopsy alone) or Arm B (fusion biopsy + standard biopsy). The primary outcome was to compare the detection rate of clinically significant prostate cancer in Arm A (n=201) vs. Arm B (n=196). The results demonstrated that no differences were found in prostate cancer, and clinically significant prostate cancer detection rates in the two arms; clinically significant prostate cancer detection rate was 60.2% vs. 60.6% in Arm A and B respectively (p=0.93). The detection rate for prostate cancer was 63.7% vs. 71.0% in Arm A and B respectively, (p=0.12). Additionally, the histopathological findings were comparable in terms of biopsy Gleason score (p=0.08), total cancer core length (p=0.06), maximum cancer core length (p=0.67), and maximum cancer core length rate (p=0.11). No adverse events were reported. The authors concluded that in biopsy naïve individuals, 7.3 % of prostate cancers are missed by fusion biopsy alone approach compared to combined fusion biopsy and standard biopsy.

In a joint consensus statement by the American Urological Association and Society of Abdominal Radiology (Rosenkrantz, 2016) regarding individuals with prostate MRI and MRI-targeted biopsy, the authors advocate the use of an MRI ultrasound fusion biopsy for repeat biopsy after a prior negative biopsy citing that obtaining concurrent systematic cores can be performed in the same session and it allows collaboration between the radiologist identifying the location of the MRI-defined targets while the urologist performs the biopsy.

The National Comprehensive Cancer Network® (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for prostate cancer (2023) notes that mpMRI can be used in staging and characterization of prostate cancer.

There has been discussion in the literature regarding whether a prostate biopsy should be done prior to mpMRI fusion with rectal ultrasound. Current peer-reviewed literature and expert consensus opinion concur that the use of mpMRI fusion techniques prior to prostate biopsy can be effective in detecting clinically significant prostate cancer that might be otherwise missed by a non-targeted biopsy. Use of mpMRI fusion with rectal ultrasound for targeted biopsy of the prostate is considered in accordance with generally accepted standards of medical practice for individuals with a persistently elevated or rising PSA when an mpMRI demonstrates at least one suspicious lesion (defined as reported on a Likert scale equal to or greater than 3, or scored equal to or greater than 3 according to the PI-RADS scoring system.

Definitions

Biopsy: The removal of a sample of tissue for examination under a microscope for diagnostic purposes.

Gleason Grading System: A prostate cancer grading system developed by the 2014 International Society of Urological Pathology (ISUP) Consensus Conference, based on the architectural features of the cancer. Numbers range from 1 to 5. The higher the number, the more undifferentiated the cancer and the more likely the cancer has extended outside of the prostate.

Gleason score: Represents the sum of the two most common Gleason grades observed by the pathologist on a specimen, the first number is the most frequent grade seen.

Magnetic resonance imaging (MRI): A diagnostic technique that uses a cylindrical magnet and radio waves to produce high quality multiplanar images of organs and structures within the body without x-rays or radiation.

Multiparametric magnetic resonance imaging (mpMRI): Combined conventional MRI with diffusion-weighted MRI (DWI), dynamic contrast-enhanced MRI (DCEI), and/or magnetic resonance spectroscopy imaging (MRSI) is known as multiparametric MRI.

Prostate Imaging Reporting and Data System (PI-RADS): Using a 1-5 score, this is a way for radiologists to report how likely it is that a suspicious area is a clinically significant cancer.

Prostate: A walnut-shaped gland that extends around the urethra at the neck of the urinary bladder and supplies fluid that goes into semen.

Prostate-specific antigen: A blood test that measures the amount of a specific prostate-related protein in blood, used to screen for prostate cancer and other conditions. A high PSA level in the blood has been linked to an increased chance of having prostate

cancer.

Transrectal ultrasound: An ultrasound test in which the sound waves are produced by a probe inserted into the rectum. Applicable to this document, the structures most commonly examined with this test are the prostate, bladder, seminal vesicles and ejaculatory ducts.

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Artemis™
BioJet™
BiopSee®
mpMRI
UroNav™
Urostation®
Virtual Navigator

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
Reviewed	05/11/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Description, Discussion/General Information and References sections.
Reviewed	05/12/2022	MPTAC review. Updated Discussion/General Information, Definitions, and References sections.
Reviewed	05/13/2021	MPTAC review. Updated Discussion/General Information and References sections. Reformatted Coding section.
Revised	05/14/2020	MPTAC review. Title change to "Prostate Biopsy using MRI Fusion Techniques." Revised MN statement; remove prostate biopsy requirement prior to imaging. Revision to NMN statement by adding "when the above criteria are not met." Updated Description, Discussion/General Information, and References sections. Updated Coding section; removed code 77021 not applicable.
Revised	02/20/2020	MPTAC review. Clarification to Clinical Indications 2nd bullet point regarding prostate biopsy(s) and 3rd bullet point regarding Likert scale and PI-RADS scoring system. Updated Discussion/General Information, Definitions, and References sections.
New	03/21/2019	MPTAC review.
New	03/20/2019	Hematology/Oncology Subcommittee review. Initial document development. Moved content of RAD.00066 Multiparametric Magnetic Resonance Fusion Imaging Targeted Prostate Biopsy to new clinical utilization management guideline document with the new title.
