Multiparametric Prostate Magnetic Resonance Imaging in the Evaluation of Prostate Cancer

Baris Turkbey, MD[1]; Anna M. Brown, MPhil[2]; Sandeep Sankineni, MD[3]; Bradford J. Wood, MD[4]; Peter A. Pinto, MD[5]; Peter L. Choyke, MD[6]

Imaging has traditionally played a minor role in the diagnosis and staging of prostate cancer. However, recent controversies generated by the use of prostate-specific antigen (PSA) screening followed by random biopsy have encouraged the development of new imaging methods for prostate cancer. Multiparametric magnetic resonance imaging (mpMRI) has emerged as the imaging method best able to detect clinically significant prostate cancers and to guide biopsies. Here, the authors explain what mpMRI is and how it is used clinically, especially with regard to high-risk populations, and we discuss the impact of mpMRI on treatment decisions for men with prostate cancer. **CA Cancer J Clin 2016;66:326-336. © 2015 American Cancer Society.**

Keywords: active surveillance, high risk, multiparametric magnetic resonance imaging (MRI), prostate cancer.

Introduction

One in every 7 men in the United States is diagnosed with prostate cancer, and approximately 27,500 deaths per year are attributed to this disease.[1] Prostate cancer represents a broad spectrum of diseases ranging from the indolent to the highly aggressive but, in general, tends to be slower growing than most other solid cancers. Screening methods based on serum prostate-specific antigen (PSA) followed by random biopsies tend to overdiagnose small indolent tumors, which begin appearing in men at a young age at autopsy and are found throughout the prostates in men ages 50 years and older. Meanwhile, larger, aggressive lesions that are outside the typical biopsy template may not be found with the strategy of PSA screening and random biopsy. This combination of PSA screening and random biopsy has yielded disappointing clinical outcomes, which have led to calls to reduce or eliminate screening for prostate cancer. The paradox of current methods is that they both overdiagnose low-risk disease and underdiagnose high-risk cancers, which led the US Preventive Health Task Force to issue a "D" grade for PSA-based screening in 2012.[2]

However, despite the failure of current screening strategies to demonstrate efficacy, death rates from prostate cancer have decreased steadily in recent years. There is concern that a policy that excludes some form of screening will result in the presentation of prostate cancer at a later and more lethal stage, reversing the gains seen recently. Several professional medical groups, such as the American Urologic Association, have advocated for the more careful use of PSA screening after thorough discussions with the patient. Missing from this debate over PSA has been the role of random biopsy. Most studies of PSA screening have focused on its low sensitivity and specificity for cancer while placing less emphasis on the unguided

[1]Staff Clinician, Molecular Imaging Program, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD; [2]Fellow, Medical Research Scholars Program, Molecular Imaging Program, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD; [3]Fellow, Molecular Imaging Program, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD; [4]Director, National Institutes of Health Center for Interventional Oncology; and Chief, Interventional Radiology Section, National Institutes of Health Clinical Center, Bethesda, MD; [5]Head, Prostate Cancer Section, Urologic Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD; [6]Program Director, Molecular Imaging Program, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

Corresponding author: Ismail Baris Turkbey, MD, 10 Center Drive, Room B3B85, Bethesda, MD 20892; turkbeyi@mail.nih.gov

DISCLOSURES: This research was made possible through the National Institutes of Health (NIH) Medical Research Scholars Program, a public-private partnership supported jointly by the NIH, and by generous contributions to the Foundation for the NIH from Pfizer Inc, the Doris Duke Charitable Foundation, the Newport Foundation, the American Association for Dental Research, the Howard Hughes Medical Institute, and the Colgate-Palmolive Company, as well as other private donors (for a complete list, please visit fnih.org/what-we-do/current-education-and-training-programs/mrsp). The NIH has a Cooperative Research and Development Agreement with Philips and InVivo as well as related shared intellectual property. Peter A. Pinto has a patent entitled Method and System for Performing Biopsies issued and a patent entitled System and Method for Planning and Performing a Repeat Interventional Procedure pending. Bradford J. Wood has a patent (US Patent 8,447,384) entitled Method and System for Performing Biopsies issued; a patent (US Patent 8731264) entitled System and Method for Fusing Real-Time Ultrasound Images With Preacquired Medical Images issued; a patent entitled System, Methods, and Instrumentation for Image-Guided Prostate Treatment issued; a patent entitled System and Method for Integrated Biopsy and Therapy pending; a patent entitled Repeat Biopsy System and Method pending; a patent entitled System and Method for Fusing Real-Time Freehand Ultrasound with Preacquired Medical Images pending; a patent entitled System and Method for Prostate Cancer Detection and Distribution Mapping pending; a patent entitled Feedback System for Integrated Interventional Planning and Navigation pending; a patent entitled Device and Method for a Trackable Ultrasound pending; a patent entitled Electromagnetically Trackable Rectal Ultrasound Transducer Needle Guide for Prostate Biopsy, Brachytherapy, or Ablation pending; and a patent entitled Multimodality Imaging System With 3-dimensional Ultrasound pending. Anna M. Brown, Baris Turkbey, Sandeep Sankineni, and Peter L. Choyke have no disclosures to declare.

doi: 10.3322/caac.21333. Available online at cacancerjournal.com

Fusion Pharmaceuticals, Inc.
Exhibit 1024.001

nature of the random biopsy. Thus, there is increasing recognition of the potential value of adding an imaging method to guide biopsy, thereby detecting larger tumors that are more likely to be clinically significant while reducing the overdiagnosis of smaller indolent cancers that are below the detection threshold of imaging. Multiparametric magnetic resonance imaging (mpMRI) has emerged as the most promising of the imaging modalities for this task. Compared with serum PSA screening and random biopsy, mpMRI with image-guided biopsy of the prostate enables direct assessment of the location, size, and stage of distinct lesions within the prostate. There is increasing recognition that it is not as important to detect *all* of the prostate cancers in a patient as it is to detect the *most aggressive* prostate cancer, generally termed the "index" lesion.[3] In this regard, the concept of "clinically significant" prostate cancer is important. Tumors that have a Gleason score of 4 + 3 (Gleason 7 prostate cancer with predominant pattern 4), tumors with a volume $\geq$0.5 cm^3, and tumors showing an aggressive pattern of invasion are all considered clinically significant because they carry a higher risk of recurrence after treatment.[4-6]

The value of adding a reliable imaging method to detect clinically significant prostate cancer mirrors the success of imaging in diagnosing many other solid tumors, in which imaging modalities such as computed tomography, ultrasound, and MRI play a major role in directing biopsies to suspicious lesions. In clinical situations, it is not uncommon for the wives of patients suspected of prostate cancer to express surprise that biopsies of the prostate are conducted randomly, when their own experience with the diagnosis of breast cancer heavily relies on the use of imaging guidance.

What is mpMRI?

An mpMRI of the prostate can be obtained in most centers that operate state-of-the-art, 1.5-Tesla (1.5T) or 3T scanners. The term "multiparametric" refers to the multiple MRI sequences that are required to make the diagnosis, which differs from other MRI scans in which the diagnosis usually depends on one essential MRI sequence. In prostate mpMRI, no one MRI sequence is definitive; rather, it is the combination of positive parameters that leads to the diagnosis. The mpMRI consists of both anatomic (T1-weighted [T1W] and T2-weighted [T2W] MRI) sequences as well as functional sequences, including diffusion-weighted imaging (DWI) MRI and dynamic contrast-enhanced (DCE) MRI.[7,8] In 2015, the American College of Radiology published guidelines for the minimum requirements for acquisition of an mpMRI of the prostate as well as a standardized reporting system known as Prostate Imaging Reporting and Data System Version 2.0 (PI-RADS 2.0).[9] mpMRI of the prostate may be acquired on either 1.5T or 3T scanners, with 3T preferred because of the higher signal-to-noise ratio, which allows for improved spatial or temporal resolution. The use of an endorectal coil (ERC) is not mandatory; however, an ERC usually improves the quality of the scan but also clearly increases the cost and discomfort of the procedure. Using an ERC improves the staging of prostate cancer, particularly for the determination of extraprostatic extension (EPE) and seminal vesicle invasion, tumor volume, and tumor laterality.[10] This improves the ability of MRI to stage prostate cancer. The increased signal provided by an ERC can be used to perform higher resolution imaging and hence better definition of the outer contours of the prostate and seminal vesicles. A meta-analysis by Engelbrecht et al suggested that use of an ERC could improve the performance of mpMRI for the local staging of prostate cancer, although they described substantial disagreement on this point in the literature because of different definitions of EPE and different MRI magnet strengths.[11] The added value of an ERC is best appreciated at 1.5T, because, at 3T, several studies have shown conflicting results regarding whether the ERC truly improves staging compared with using phased-array surface coils alone.[10,12-14] Cornud et al reported a reduction in understaging of prostate cancer from 42% to 22% with use of an ERC at 1.5T with 96% specificity for EPE.[15] While controversy still exists about the benefit of using an ERC, most experts agree that an ERC is not necessary for a purely diagnostic mpMRI of the prostate; however, it becomes more useful for local staging.[10,16] An mpMRI does not require any specific preparation on the part of the patient, but the usual MRI precautions regarding metallic implants and contraindications to gadolinium-based contrast agents must be observed (Table 1).

An mpMRI consists of a series of pulse sequences, each of which contributes to the overall diagnosis. Because many patients come to mpMRI after a prior biopsy, the T1W MRI is mainly used to detect biopsy-related, residual hemorrhage that can obscure cancers, thus decreasing the accuracy of mpMRI. Typically, a delay of 6 to 8 weeks after biopsy is recommended; but even with this delay, significant hemorrhage may be discovered, and, if present, the examination should be rescheduled. On T2W MRI, the zonal architecture of the prostate becomes readily defined, including identification of the peripheral zone, transition zone, prostatic urethra, prostatic capsule, and seminal vesicles. In addition to showing the anatomy, T2W MRI is useful for delineating suspicious lesions because of their shorter "T2 relaxation time" compared with normal glandular tissue, which makes lesions appear darker than the normal peripheral zone, although slightly brighter and more homogeneous than the normal transition zone. Moreover, because of the higher resolution of T2W

Fusion Pharmaceuticals, Inc.
Exhibit 1024.002

TABLE 1. Multiparametric Magnetic Resonance Imaging Optimization

CLINICAL USE	ENDORECTAL COIL	T2W	DWI WITH HIGH B-VALUE	DCE
Screening/detection		Yes	Yes	
Characterization	Yes	Yes	Yes	Yes
Localization/staging	Yes	Yes		
Active surveillance		Yes	Yes	
Post-RARP and recurrence	Yes	Yes	Yes	Yes

DCE indicates dynamic contrast enhanced; DWI, diffusion-weighted imaging; RARP, robot-assisted radical prostatectomy; T2W, T2-weighted.

sequences, they are best at establishing the anatomic relation of the tumor with critical structures, such as the prostatic capsule and neurovascular bundles.[17] T2W sequences tend to have moderate sensitivity (range, 58%-71%) but relatively higher specificity (range, 77%-98%) for cancer,[18-20] although the diagnostic accuracy of T2W MRI is improved by the other functional sequences, such as DWI MRI and DCE MRI, which are considered simultaneously by imagers as they examine anatomic T2W images.

Distinct from the "anatomic" sequences, the "functional" mpMRI sequences are comprised of DWI MRI and DCE MRI.[21] The DWI reflects the degree of water diffusion in the prostate. Cancers, because of their tightly packed cells and dense surrounding stroma, have impeded water diffusion compared with normal parenchyma. Hence, their apparent diffusion coefficient (ADC), reflecting the diffusivity of water, is lower than that in normal tissue. The ADC is derived by obtaining images at different magnetic gradient strengths, commonly referred to as "b-values." A very valuable additional DWI sequence is the "high b-value" image capable of detecting significant water diffusion restriction in tumors, which appear bright against the background tissue in the high b-value image, with its very low signal, creating a "hotspot" image that is quite useful, even if it is often noisy because of the lower signal-to-noise ratio. DWI is the recommended dominant sequence in PI-RADS 2.0 for the peripheral zone, where the majority of prostate cancers occur. The degree of diffusion restriction reflects the aggressiveness of the prostate cancer, with lower ADCs associated with higher grade tumors.[21,22] However, the ADC value is not sufficient to characterize prostate lesions, as there is considerable overlap among cancers of different Gleason scores with regard to their ADC. The addition of DWI to the T2W MRI has been shown to significantly increase both the sensitivity and the specificity of mpMRI. Combined with T2W MRI, DWI has been reported to have a sensitivity of approximately 80% and a specificity of 81% for clinically significant prostate cancer.[23]

DCE MRI is another functional sequence that provides valuable information to characterize lesions seen on mpMRI. DCE MRI is obtained before, during, and after the injection of intravenous gadolinium-based contrast media and is followed by rapid, 3-dimensional, T1W sequences that are sensitive to detecting the arrival of the contrast agent in the tumor. Focal early hyperenhancement is suggestive of a malignancy, but there is considerable overlap with benign conditions, such as benign prostatic hyperplasia and prostatitis.[24,25] DCE MRI is most helpful when the T2W MRI and DWI are equivocal. In these cases, strong early enhancement or rapid washout of contrast media from the lesion increases the suspicion that the lesion is a clinically significant malignancy. DCE MRI has also been very useful in detecting sites of recurrent prostate cancer after prostatectomy or radiation therapy where focal enhancement may indicate a site of focal recurrence.

There is currently debate in the literature about the utility of DCE MRI in prostate cancer detection. Earlier studies showed significant gains in the accuracy of prostate lesion detection by incorporating DCE MRI into an mpMRI protocol. For example, Tanimoto et al reported an increase in the area under the curve from 0.905 to 0.966 for detecting prostate cancer with the addition of DCE MRI to T2W and DWI MRI on a 1.5T scanner in a cohort of patients with elevated PSA.[26] The main arguments against using DCE MRI center around questioning the incremental gain in detection when T2W and DWI MRI already perform very well in detecting clinically significant lesions in the context of the added cost, scanner time, and patient inconvenience and discomfort of the DCE MRI sequence.[27] This is a reasonable way to decrease costs in patients who present for routine cancer detection using MRI as a complement to biopsy; however, in patients who are postprostatectomy or postradiation, DCE MRI should be used, because it may be the only way to detect recurrent disease in these patients with altered anatomy in the form of enhancement within scar tissue.[27-30]

mpMRI-Transrectal Ultrasound Fusion Biopsies

The most important clinical value of mpMRI is in directing biopsies into abnormal areas. PI-RADS 2.0 is an international system of scoring MRI lesions on a scale from 1 to 5. Lesions judged to be 1 or 2 do not require biopsy, whereas lesions scored at 4 or 5 require biopsy. A score of 3 indicates a lesion that may require biopsy, depending on clinical factors. Recent technologies permit the fusion of mpMRI to real-time transrectal ultrasound (TRUS). This enables the performance of image-guided biopsy of the prostate outside the MRI suite under TRUS and enables far more biopsies to be obtained than would be possible if the biopsy were limited to MRI-in-gantry biopsies, which are

Fusion Pharmaceuticals, Inc.
Exhibit 1024.003

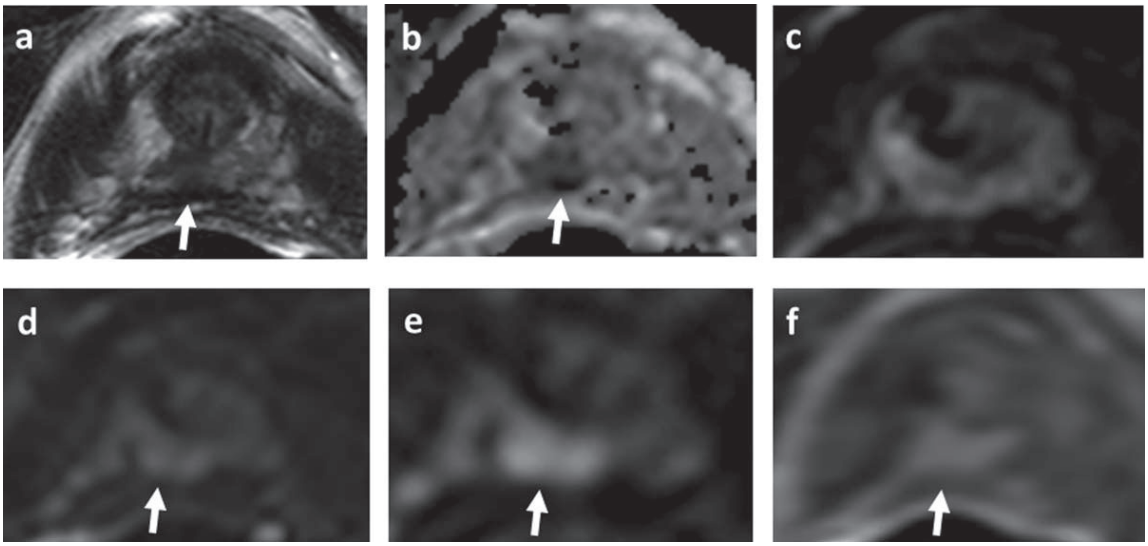

FIGURE 1. A 70-Year-Old Biopsy-Naïve Patient With a Prostate-Specific Antigen (PSA) Level of 9.97 ng/mL Underwent Initial Multiparametric Magnetic Resonance Imaging (mpMRI) Evaluation. (a) Axial T2-weighted images identify an area of low signal intensity in the midline distal apical peripheral zone (arrow). (b) Axial apparent diffusion coefficient maps of diffusion-weighted imaging (DWI) identify the hypointense lesion in the same midline apical peripheral zone location (arrow). The lesion is invisible on (c) low b-value (b = 560) DWI and (d) is barely visible on b = 1000 DWI (arrow); however, (e) the high b-value DWI (b = 2000) shows the entire lesion as a hyperintense signal focus at the same location (arrow) (f) Dynamic contrast-enhanced image shows an early, focal hyperenhancing lesion in the midline apical peripheral zone (arrow). The patient underwent robotic-assisted radical prostatectomy, at which final pathology confirmed Gleason 4 + 4 disease. At 3-month postsurgical follow–up, the patient had a PSA of <0.01 ng/mL.

technically complex. Typically, the new fusion devices register the mpMRI to the TRUS image, allowing the operator to use the real-time aspects of TRUS to perform the biopsy while using the superior diagnostic features of mpMRI to target the lesion. Such biopsies have allowed more accurate localization of prostate tumors and better clinical management of patients with clinically significant prostate cancer. A recent report in a cohort of 1003 men demonstrated that there was a 30% increased detection rate of high-risk prostate cancer and a 17% decrease in the detection of low-risk prostate cancer when an MRI/TRUS fusion-guided, targeted biopsy system was compared with standard TRUS biopsy.[31] Therefore, mpMRI of the prostate and targeted biopsy reduce the overdiagnosis of indolent disease that otherwise would have led to overtreatment while at the same time increasing the detection of clinically significant prostate cancers, many of which would have been missed by random biopsy. Similar results have been reported by other institutions[32-37]

TRUS biopsy alone tends to oversample the posterior aspect of the prostate, whereas regions such as the anterior, distal apical, midline, and subcapsular prostate are frequently undersampled[38-43] (Fig. 1). These challenging areas may harbor clinically significant disease and can alter clinical management. An important example is the "prostatic evasive anterior tumor syndrome" (PEATS), which describes the phenomenon of anterior tumors commonly being missed with TRUS-guided biopsy[38] (Fig. 2). Although MRI/TRUS fusion biopsy is the most widely used method of combining mpMRI with prostate biopsy, several other image-guided biopsy techniques are also in use.[44] One approach is the in-gantry MRI-guided prostate biopsy, which involves obtaining biopsy samples under direct MRI guidance in the MRI gantry. The main advantage of this approach is that it enables accurate lesion sampling, because a confirmatory MRI showing the biopsy needle inside the target lesion can be easily obtained. In-bore biopsies can have very high prostate cancer detection rates, ranging from 81% to 93% for clinically significant disease.[45] However, compared with the fusion method, the procedure is long, resource-intensive, and uncomfortable, requiring the patient to lie prone in the MRI for protracted periods. Moreover, all equipment, including needles, must be nonmagnetic, which increases the cost and risk management of the procedure. Another approach is to simply use the MRI to visually guide the TRUS biopsy on a standard ultrasound machine without software-based image fusion. This has been termed "cognitive fusion," as it requires the operator to mentally fuse the MRI to the ultrasound. This method can be quite satisfactory in the right hands. For instance, in a trial of 555 patients, cognitive fusion biopsy showed improved detection accuracy for clinically significant cancers over the 12-core TRUS biopsy ($P < .001$). Furthermore, the cognitive fusion-targeted biopsy more accurately estimated tumor burden ($P = .002$) while detecting 16% more high-grade (Gleason pattern 4 and 5) cases.[46] However, not all operators are as facile with cognitive fusion, and it is difficult to teach. Thus, various methods permit the results of the mpMRI to guide subsequent prostate biopsy; however, the most efficient is probably the MRI-TRUS fusion method.

Fusion Pharmaceuticals, Inc.
Exhibit 1024.004

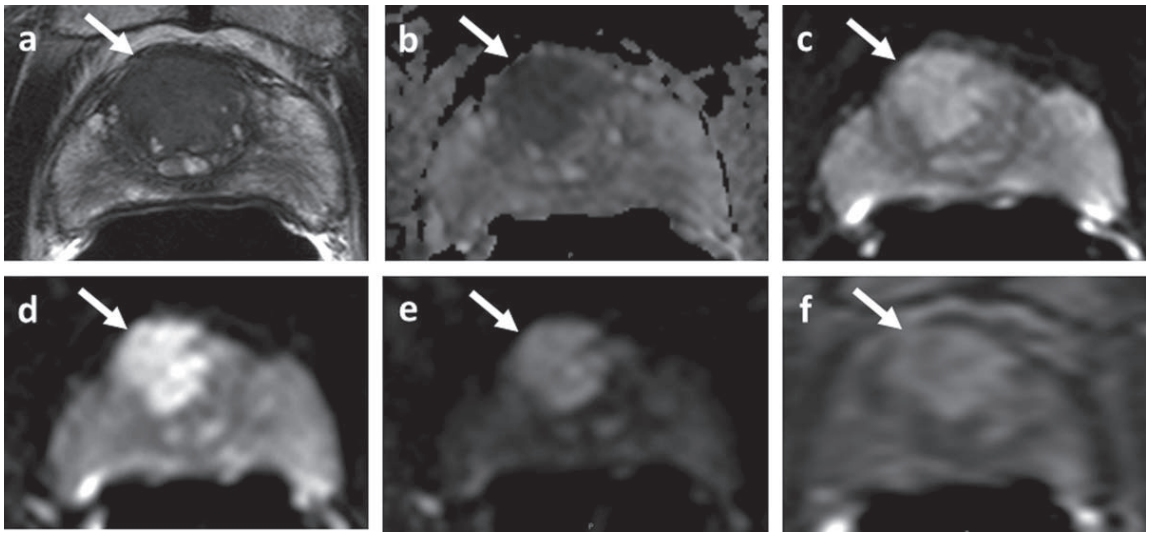

FIGURE 2. A 65-Year-Old African American Male Presenting With a Prostate-Specific Antigen (PSA) Level of 14.91 ng/mL Elected to Undergo Multiparametric Magnetic Resonance Imaging (mpMRI) for Further Evaluation. He had a positive family history for early diagnosed prostate cancer in a first-degree relative and history of 4 prior negative biopsies (using the standard of care transrectal ultrasound [TRUS] approach). (a) An axial T2-weighted image shows a large midline-to-right apical base, anterior transition zone lesion (arrow). (b) Axial apparent diffusion coefficient map of diffusion-weighted imaging (DWI) identifies the large anterior lesion with strong hypointense appearance (arrow). (c) Lower b-value DWI (b = 560) (arrow) and (d) intermediate b-value (b = 1000) DWI (arrow) show the lesion; however, (e) high b-value DWI (b = 2000) highlights the large anterior lesion with strong enhancement and suppression of the normal prostate tissue (arrow). (f) Axial dynamic contrast-enhanced image shows an early, large, focal hyperenhancement of the same lesion (arrow). The patient underwent targeted MRI/TRUS fusion-guided biopsy along with standard of care biopsy. The biopsy resulted in 1 of 12 TRUS cores positive and 3 of 4 MRI/TRUS-guided biopsy cores positive, and the highest Gleason score was 4 + 4 (25%). The patient elected to undergo robotic-assisted radical prostatectomy, and final wholemount histopathology confirmed a Gleason 4 + 4 pattern in 40% of the prostate with a secondary Gleason 4 + 5 pattern.

The biopsy approach can also be transperineal, which is accepted as safer when possible sepsis-related complications of the transrectal approach are considered.[47,48] Aside from how the needle is placed in the prostate, whether perineal or transrectal, MRI plays a major role in identifying the target lesion(s) and guiding the needle path.

The positive predictive value of mpMRI-guided biopsy depends on the population studied. To date, most studies have been conducted at single institutions, so it is difficult to compare results across centers. For instance, a recent comprehensive review of studies from 2000 to 2014 found a wide range of sensitivity values (range, 44%-87%) for detecting clinically significant prostate cancer in biopsy-naïve patients or those who have undergone prior negative biopsies. This reflects the use of various technologies, validation methods, and patient populations. However, most studies consistently report a high negative predictive value for MR-guided biopsies in excluding clinically significant disease.[49] A high negative predictive value is meaningful as it increases the confidence that there is little chance of clinically significant or actionable disease in patients who have a negative mpMRI-guided biopsy; however, a negative MRI should not preclude biopsy that would otherwise be clinically indicated.[50-54]

The accuracy of mpMRI-guided biopsies depends to a large extent on the ability to observe lesions on mpMRI. Prior studies have described "MRI-invisible" lesions as those in which lesions are found on 12-core systematic biopsy or on radical prostatectomy but are missed by fusion biopsy. In a study of biopsy-naïve men, Salami et al showed that the cancer detection rate for MRI/ultrasound fusion biopsies was only 52.1% compared with the overall detection rate of 65% for the combination of fusion and 12-core systematic biopsy results.[36] Another study by Le et al showed that the best results were obtained with the combination of systematic and fusion biopsies when comparing biopsy results with wholemount radical prostatectomy specimens. In their study, Le and colleagues showed a per-core cancer detection rate of 42% for targeted biopsy compared with 20% for systematic biopsy but an 81% rate of detecting the highest Gleason pattern for the combination of biopsies compared with only 54% for each individual method.[55] Thus, the authors concluded that both methods were needed to achieve the highest predictive accuracy. Both of these studies examined the cancer detection rate in depth but did not provide as clear of an answer for the negative predictive value. Because fusion biopsies are performed for mpMRI-visible lesions, the true negative predictive value for mpMRI is not yet certain.

Clinical Indications for mpMRI

The exact rules regarding the use of mpMRI in prostate cancer are yet to be defined. For the most part, it is used in

Fusion Pharmaceuticals, Inc.
Exhibit 1024.005

conjunction with an elevated PSA value to further define the extent and location of disease. Few currently advocate it as a primary screening method. Nonetheless, there is widespread agreement that the following scenarios benefit from the addition of mpMRI:

1) Biopsy-Naïve Patients With Elevated PSA and/or Positive Digital Rectal Examination With or Without Positive Lower Urinary Tract Symptoms Before a Biopsy Decision

Here, a positive mpMRI may define a lesion that should undergo image-guided biopsy. In the appropriate settings, a negative mpMRI may enable the patient to defer a biopsy and return to PSA surveillance. High-risk populations (African American [AA] men or patients with a family history of prostate cancer) may also benefit from early screening with mpMRI.

2) Previous Negative Biopsies Despite Rising PSA

Here, a positive mpMRI may point to a lesion that may have been missed on previous biopsies or provide an explanation (benign prostatic hyperplasia, prostatitis) for a rising PSA in the absence of cancer.

3) Previous Positive Biopsy for Cancer

Here, a positive mpMRI may be useful in guiding biopsy and staging the cancer (demonstrating EPE or seminal vesicle invasion), thereby assisting treatment planning, while a negative or minimally abnormal mpMRI may suggest that active surveillance (AS) is a possible management strategy in the right clinical circumstances (low-volume, low-grade tumors or limited life expectancy). However, even a negative mpMRI carries some risk of a high-grade cancer; therefore, patients need to be followed carefully with PSA and mpMRI to avoid missing such tumors.

4) A Rise in PSA After Definitive Therapy (Biochemical Recurrence After Surgery or Radiation)

Here, a positive mpMRI can help identify the site of recurrence.

Impact of mpMRI on Treatment Decisions

Regardless of the clinical scenario leading to an mpMRI, there are specific implications for positive and negative studies. Recent clinical studies have evaluated the role of mpMRI in guiding therapeutic approaches, both for patients undergoing radical prostatectomy and definitive radiation therapy and for those considering AS. mpMRI holds particular promise to select patients eligible for AS and in conjunction with targeted biopsy to monitor specific lesions over time. The use of other clinical parameters, such as race and family history, may help determine a personalized screening and monitoring plan for higher risk patient populations.

Utility of mpMRI for Surgical and Radiation Planning

Multiple studies have shown the value of mpMRI as an aid in planning surgical and radiation treatments. For instance, identification of the index lesion can assist in decision making before radical prostatectomy. mpMRI is helpful in defining where margins may be positive, so that wider excisions are performed at those sites while the opposite, less involved side of the prostate may be spared neurovascular bundle excision or at least partial nerve sparing may be performed during surgery. This can improve postoperative erectile function.[56,57] mpMRI can alter the surgical approach in as many as 30% of cases in which it is performed.[58]

Similar to its utility in assisting with surgical planning, prostate mpMRI has also shown utility in altering radiation therapy planning. For instance, radiation oncologists use mpMRI to create more accurate target volume delineation, calculate radiation dose, and decide on the duration of adjuvant androgen-deprivation therapy in almost 20% to 40% of cases.[59] The imaging findings most commonly leading to altered therapy are the presence of extracapsular extension (ECE) and/or seminal vesicle invasion and lymph node involvement. However, clear evidence of a survival benefit to these treatment modifications is lacking, and longer term follow-up in controlled studies will be needed to assess the impact.

mpMRI in AS

The decision to embark on AS is an important one. It may significantly improve quality of life without putting the patient at risk for metastatic disease. Many prostate cancers that are of low grade and of low volume do not progress, at least not fast enough to affect the longevity of a patient, especially in the presence of life-shortening comorbidities (heart disease, stroke, and complications resulting from long-standing diabetes and hypertension). However, inappropriately placing a patient on AS can put the patient at risk for metastatic disease. mpMRI can be very helpful in informing the decision to begin AS. Once a patient is identified as a potential AS candidate on routine random biopsy, an mpMRI is obtained to confirm that the tumor is, in fact, low volume. One study found that prostate mpMRI combined with clinical features performed much better than clinical features alone in predicting which patients could be safely directed to AS.[60] Prostate mpMRI performed better than any of the conventional clinical assessment scoring systems—D'Amico, Epstein, and Cancer of the Prostate Risk Assessment—in predicting candidates for AS.

Fusion Pharmaceuticals, Inc.
Exhibit 1024.006

Approximately one-third of initial candidates for AS are upgraded on MRI/TRUS fusion biopsy. This number corresponds to the patients who eventually fall off AS within several years when mpMRI is not initially performed. Long-term data are still lacking on the value of mpMRI in monitoring patients on AS, but several centers have ongoing long-term studies investigating the role of mpMRI in monitoring patients on AS, allowing negative or stable mpMRIs to substitute for the repeated follow-up biopsies that are required in most AS protocols. If these studies demonstrate the effectiveness and safety of this approach, mpMRI could be used as a surrogate for biopsy in the future. The optimal surveillance frequency for previously MRI/TRUS-biopsied lesions is estimated to be at least 2 years, although large-scale, multiinstitutional data are lacking to support a clear recommendation.[61] Finally, although some groups reported low levels of anxiety during AS,[62] it is still associated with anxiety among some patients. Close monitoring of such patients may also contribute to reducing this anxiety and allow patients to continue on AS longer. When monitoring patients on AS, it is important to track the PI-RADS score of suspicious lesions. Prior studies have shown that the PI-RADS score was a significant predictor of prostate cancer ($P < .05$ for overall and clinically significant) on univariate and multivariate analysis, whereas clinical factors like digital rectal examination (DRE) and prostate volume were not,[63] and that using a PI-RADS score of ≥ 4 for cancer detection would have missed only 3.5% of clinically significant cancers as defined by Epstein's criteria using targeted biopsy.[36]

Identifying High-Risk Tumors With mpMRI

In addition to being potentially useful for monitoring patients on AS, mpMRI can identify features that may confer a worse prognosis, such as large lesion size, ECE, and seminal vesicle invasion, corresponding to the T-classification of the tumor. The value of mpMRI with regard to predicting ECE has been extensively studied. Multiple recent studies have shown that prostate mpMRI is helpful but imperfect in the prediction of ECE.[64,65] For instance, mpMRI has been shown to have a higher accuracy for determining ECE compared with clinical Partin tables (a nomogram based on clinical factors alone). Prostate mpMRI was particularly useful when it was negative for ECE, as the negative predictive value was >90%.[66] However, microscopic ECE may be difficult to detect on mpMRI. Overall, the recent literature reflects encouraging results for using mpMRI to better characterize features that portend a poor prognosis like ECE, thus aiding physicians' treatment decisions.

There are limitations to mpMRI in defining the exact contours of the cancer. Although there is a correlation between lesion volume and pathologic volume, there can be mismatches related to the reduced detection of the growing margin of the tumor. In addition, the false-negative rate for mpMRI remains approximately 5%.[67] Prostate cancers can be discontinuous, meaning that nests of cancer are separated by normal parenchyma. In those patients, the cancer becomes undetectable on mpMRI. In such patients, careful attention to PSA kinetics might suggest that a larger but sparse tumor has been missed by mpMRI and that a 12–core, random TRUS biopsy might be of benefit.

Use of mpMRI for Predicting, Localizing, and Treating Biochemical Recurrence

Despite best efforts, a significant fraction of patients with prostate cancer who undergo surgery or radiation will recur. This biochemical recurrence (BCR) is first detected by rising PSA values. Before treatment, mpMRI may provide clues regarding the risk of BCR by combining both clinical factors and imaging findings. For instance, mpMRI combined with clinical factors (clinical stage, PSA, and biopsy Gleason score) led to higher hazard ratios for BCR.[68,69]

Prostate mpMRI may be useful not only in predicting patients at high risk for BCR based on pretreatment imaging but also in identifying specific sites of recurrence once they occur.[70] Thus, prostate mpMRI is playing a growing role in patients with recurrent prostate cancer. Although the majority of men are cured by surgery or radiation therapy, from 15% to 30% experience BCR. PSA is a sensitive surrogate marker of prostate cancer recurrence.[71] Recurrent disease can give rise to progressive and metastatic disease and, thus, is often treated, although there is a degree of uncertainty over whether the recurrence represents local, lymph node, or distant disease. Therefore, there is great interest in intercepting the disease early after recurrence is detected. DCE MRI is the most valuable sequence on mpMRI for determining recurrent prostatic disease followed by T2W imaging. Treatment with either surgery or radiation alters the anatomy and stroma, so that DWI imaging is less useful.[72] Because of the distorted anatomy after definitive therapy, the use of an ERC is recommended in detecting BCR with mpMRI of the prostate. DCE MRI with early enhancement and washout of contrast media is predictive of recurrence, even with relatively low PSA values (<1 ng/mL).

Another future potential consideration with respect to BCR is using mpMRI to guide therapeutic strategies to treat focal areas of recurrent disease.[73] Once a patient is known to have recurrent prostate cancer because of a rising PSA level or other clinical measures, it is important to localize the recurrent disease before devising treatment plans.[74] The ability of mpMRI to reliably identify focal areas of recurrent prostate cancer has changed the landscape

Fusion Pharmaceuticals, Inc.
Exhibit 1024.007

of treatment options such that therapeutic strategies like focal salvage radiation are possible.[72] Although the evidence remains limited and focal therapeutic approaches are still experimental in nature at this stage, in centers investigating these new methods, mpMRI has a promising role for planning other focal salvage therapy strategies, such as high-intensity focused ultrasound.[75] Of course, it is important that mpMRI be used in conjunction with targeted biopsies; because, despite the high diagnostic accuracy of mpMRI in localizing recurrent disease, actual biopsy results change the target delineation in over 50% of patients.[76] Moreover, imaging features are inherently nonspecific and can also occur in granulation or healing tissue. Overall, mpMRI of the prostate has an important role in identifying small local foci of recurrent disease in the prostatic fossa after treatment to assist with further salvage management strategies, although this is still in the realm of clinical research rather than a standard of care.

Use of mpMRI in High-Risk Patient Populations

AA men and men with a strong family history of prostate cancer are at higher risk for aggressive prostate cancer, placing an even higher premium on accurate diagnosis and staging. In a cohort of 1801 men undergoing prostatectomy (including 256 AA men), there was a nearly 2-fold increase in the upgrading of clinical disease in AA men (27.3% vs 14.4%; $P < .001$) and a significantly increased rate of positive surgical margins (9.8% vs 5.9%; $P = .02$).[77] These findings were corroborated in a later study that showed increased recurrence rates among 234 AA men compared with the entire group of 1231 patients, even in men with low-grade disease (Gleason ≤ 6; hazard ratio, 2.01; 95% confidence interval, 1.08-3.72; $P = .029$).[78] A recent study showed that AA men were at higher risk of seminal vesicle invasion with rates of 51% for AA men versus 30% for Caucasian men ($P = .01$) in a group of 1104 patients.[78] These and other findings suggest that AA men may particularly benefit from mpMRI. One study of prostatectomy specimens in 196 men (87 black and 89 white) suggested significant disparities in the burden, aggressiveness, and location of disease between AA and Caucasian men. Compared with white men, black men were 32% more likely to have significant cancer, 26% more likely to have Gleason 7 or higher disease, and had a 22% higher rate of anteriorly located index lesions (Fig. 2). In patients who had pathologic upgrading from ultrasound-guided biopsy to final prostatectomy, the dominant lesion was more often anteriorly located in AA men (59% vs 0%).[79] It has been shown that anteriorly located lesions are often better identified by mpMRI, and patients with anterior lesions may stand to benefit the most by using such options.[39,40,43] Thus, mpMRI may be particularly valuable for AA men with prostate cancer to identify the anterior lesions. It is important to note, however, that AA men may have difficulty with obtaining mpMRI because of existing disparities in health care access.

Another population at risk for aggressive disease is patients with a strong family history of prostate cancer. While hereditary forms of prostate cancer comprise only a small fraction of total prostate cancers (<10%),[80] it has been shown that these men are at increased risk of developing prostate cancer at a younger age.[81] Thus, for patients with a strong family history, it may be helpful to adjust screening paradigms to detect the cancer at a more curable stage. Prior attention has focused on using PSA and DRE for early detection of prostate cancer in at-risk men with a strong family history[82]; however, it is conceivable that, as screening practices continue to evolve, mpMRI may have a role in detection and treatment strategies for these patients. In fact, a recent study by deSouza et al showed that ERC T2W MRI and DWI at 3T may serve as a new screening tool in patients at higher genetic risk for prostate cancer.[83] While the methods and paradigms for appropriate patient selection are still emerging, mpMRI may provide utility in helping identify lesions in higher risk patients and monitoring these patients over time.

AS in High-Risk Populations

Given the increased likelihood of aggressive disease in high-risk populations, it is not surprising that there is controversy regarding AS in these populations. Guidelines for AS with mpMRI in a high-risk cohort have not been established. The decision to use mpMRI is determined on a case-specific basis and must be made with the full understanding of the patient based on prior clinical evaluation (symptoms, rising PSA, positive DRE, family history) and biopsy findings. It may be particularly important to perform mpMRI at the onset of AS, because AA men have higher rates of AS discontinuation even when controlling for clinical parameters and socioeconomic status.[84] This may be explained by the more aggressive prostate cancers afflicting AA men.[85-87] The question has also been raised regarding whether AA men should be on AS at all because of their higher adverse outcome rates, even for patients with apparently low-risk prostate cancer.

Future Applications of mpMRI

There are several challenges facing prostate mpMRI. First, the existing clinical data, although very compelling, cannot be characterized as "Level 1" evidence, as it is largely derived from single-institution studies. Larger, multiinstitutional studies are needed before mpMRI becomes the standard of care. Clearly, mpMRI is expensive; and, in a cost-cutting medical environment, clear evidence of efficacy

Fusion Pharmaceuticals, Inc.
Exhibit 1024.008

and cost effectiveness will need to be presented to decision-makers. By reducing the invasiveness (no ERC) and number of sequences (eg, eliminating DCE MRI), it may be possible to reduce the cost of MRI so that it will have a favorable cost-benefit ratio.

An important question not completely addressed by the current literature is whether mpMRI can predict the biological aggressiveness of a prostate cancer. If this could be reliably established, the decision to undergo AS or radical treatment could be based on several parameters, such as serum PSA, PSA density, Gleason score, and mpMRI. Prostate mpMRI has been reported to predict more aggressive disease mainly based on ADC maps derived from DWI.[23,88,89] Recently, image processing based approaches such as computer-aided diagnosis systems and texture analysis, also referred to as *radiomics*, are being explored to investigate whether imaging can predict tumor aggressiveness. Prostate mpMRI will likely never replace a biopsy; however, mpMRI can provide data about the risk of aggressiveness of prostate cancer, and this can potentially be used in conjunction with clinical variables for risk stratification and decision making.

The superior anatomic resolution of mpMRI permits the detection of clinically significant prostate cancer lesions. This has enabled the use of mpMRI to guide focal therapy of prostate cancer through one of several minimally invasive techniques, such as high-intensity focused ultrasound, cryotherapy, laser ablation, and irreversible electroporation.[90-92] MRI technology not only allows physicians to reach the focal lesions for therapy but also allows them to monitor the status of treatment in real time via MRI thermometry, which results in accurate tumor damage estimation.[93-97] The early and limited results for focal therapy are promising; however, these methods are still under development, and large-scale, multiinstitutional studies are needed to determine their efficacy and side effects.

Conclusions

The role of mpMRI in prostate cancer is rapidly evolving. Prostate mpMRI is being used not only to localize and stage prostate cancer but also to establish candidates for AS. Combined with image-guided biopsy, mpMRI will help physicians accurately tailor treatment options, such as AS, surgery, radiation, and even focal therapy. Further research will hopefully allow the identification of patients with clinically significant disease who are at risk of a less favorable clinical outcome to receive more aggressive therapy early in the course of disease while reducing the intensity of treatment for those at lower risk. Thus, mpMRI of the prostate should play a major role in the precision therapy of prostate cancer. ■

References

1. American Cancer Society. Cancer Facts & Figures 2014. Atlanta, GA; American Cancer Society; 2014.
2. Moyer VA; US Preventive Services Task Force. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2012; 157:120-135.
3. Turkbey B, Choyke PL. Decade in review-imaging: a decade in image-guided prostate biopsy. *Nat Rev Urol.* 2014;11:611-612.
4. Stamey TA, McNeal JE, Yemoto CM, Sigal BM, Johnstone IM. Biological determinants of cancer progression in men with prostate cancer. *JAMA.* 1999;281:1395-1400.
5. Ploussard G, Epstein JI, Montironi R, et al. The contemporary concept of significant versus insignificant prostate cancer. *Eur Urol.* 2011;60:291-303.
6. Chamie K, Sonn GA, Finley DS, et al. The role of magnetic resonance imaging in delineating clinically significant prostate cancer. *Urology.* 2014;83:369-375.
7. Esen T, Turkbey B, Patel A, Futterer J. Multiparametric MRI in prostate cancer [serial online]. *Biomed Res Int.* 2014;2014:296810.
8. Turkbey B, Albert PS, Kurdziel K, Choyke PL. Imaging localized prostate cancer: current approaches and new developments. *AJR Am J Roentgenol.* 2009;192:1471-1480.
9. American College of Radiology. MR Prostate Imaging Reporting and Data System, Version 2.0. acr.org/~/media/ACR/Documents/PDF/QualitySafety/Resources/PIRADS/PIRADS V2.pdf. Accessed April 1, 2015.
10. Gupta RT, Kauffman CR, Polascik TJ, Taneja SS, Rosenkrantz AB. The state of prostate MRI in 2013. *Oncology (Williston Park).* 2013;27:262-270.
11. Engelbrecht MR, Jager GJ, Laheij RJ, Verbeek AL, van Lier HJ, Barentsz JO. Local staging of prostate cancer using magnetic resonance imaging: a meta-analysis. *Eur Radiol.* 2002;12:2294-2302.
12. Kim BS, Kim TH, Kwon TG, Yoo ES. Comparison of pelvic phased-array versus endorectal coil magnetic resonance imaging at 3 Tesla for local staging of prostate cancer. *Yonsei Med J.* 2012;53:550-556.
13. Heijmink SW, Fütterer JJ, Hambrock T, et al. Prostate cancer: body-array versus endorectal coil MR imaging at 3 T–comparison of image quality, localization, and staging performance. *Radiology.* 2007;244:184-195.
14. Lee SH, Park KK, Choi KH, et al. Is endorectal coil necessary for the staging of clinically localized prostate cancer? Comparison of non-endorectal versus endorectal MR imaging. *World J Urol.* 2010;28:667-672.
15. Cornud F, Belin X, Flam T, et al. Local staging of prostate cancer by endorectal MRI using fast spin-echo sequences: prospective correlation with pathological findings after radical prostatectomy. *Br J Urol.* 1996;77: 843-850.
16. Heenan SD. Magnetic resonance imaging in prostate cancer. *Prostate Cancer Prostatic Dis.* 2004;7:282-288.
17. Weinreb JC, Blume JD, Coakley FV, et al. Prostate cancer: sextant localization at MR imaging and MR spectroscopic imaging before prostatectomy. *Radiology.* 2009;251: 122-133.
18. Delongchamps NB, Rouanne M, Flam T, et al. Multiparametric magnetic resonance imaging for the detection and localization of prostate cancer: combination of T2-weighted, dynamic contrast-enhanced and diffusion-weighted imaging. *BJU Int.* 2011; 107:1411-1418.
19. Turkbey B, Mani H, Shah V, et al. Multiparametric 3T prostate magnetic resonance imaging to detect cancer: histopathological correlation using prostatectomy specimens processed in customized magnetic resonance imaging based molds. *J Urol.* 2011; 186:1818-1824.
20. De Rooij M, Hamoen EH, Fütterer JJ, Barentsz JO, Rovers MM. Accuracy of multiparametric MRI for prostate cancer detection: a meta-analysis. *AJR Am J Roentgenol.* 2014;202:343-351.
21. Sankineni S, Osman M, Choyke PL. Functional MRI in prostate cancer detection [serial online]. *Biomed Res Int* 2014: 590638, 2014.
22. Gibbs P, Tozer DJ, Liney GP, Turnbull LW. Comparison of quantitative T2 mapping and diffusion-weighted imaging in the normal and pathologic prostate. *Magn Reson Med.* 2001;46:1054-1058.
23. Turkbey B, Shah V, Pang Y, Bernardo M. Is apparent diffusion coefficient associated with clinical risk scores for prostate cancers

Fusion Pharmaceuticals, Inc.
Exhibit 1024.009

that are visible on 3T MR images? *Radiology*. 2011;258:488-495.

24. Oto A, Yang C, Kayhan A, et al. Diffusion-weighted and dynamic contrast-enhanced MRI of prostate cancer: correlation of quantitative MR parameters with Gleason score and tumor angiogenesis. *AJR Am J Roentgenol*. 2011;197:1382-1390.
25. Hara N, Okuizumi M, Koike H, Kawaguchi M, Bilim V. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a useful modality for the precise detection and staging of early prostate cancer. *Prostate*. 2005;62:140-147.
26. Tanimoto A, Nakashima J, Kohno H, Shinmoto H, Kuribayashi S. Prostate cancer screening: the clinical value of diffusion-weighted imaging and dynamic MR imaging in combination with T2-weighted imaging. *J Magn Reson Imaging*. 2007;25:146-152.
27. Puech P, Sufana-Iancu A, Renard B, Lemaitre L. Prostate MRI: can we do without DCE sequences in 2013? *Diagn Interv Imaging*. 2013;94:1299-1311.
28. Panebianco V, Sciarra A, Lisi D, et al. Prostate cancer: 1HMRS-DCEMR at 3T versus [(18)F]choline PET/CT in the detection of local prostate cancer recurrence in men with biochemical progression after radical retropubic prostatectomy (RRP). *Eur J Radiol*. 2012;81:700-708.
29. Boonsirikamchai P, Kaur H, Kuban DA, Jackson E, Hou P, Choi H. Use of maximum slope images generated from dynamic contrast-enhanced MRI to detect locally recurrent prostate carcinoma after prostatectomy: a practical approach. *AJR Am J Roentgenol*. 2012;198:W228-W236.
30. Casciani E, Polettini E, Carmenini E, et al. Endorectal and dynamic contrast-enhanced MRI for detection of local recurrence after radical prostatectomy. *AJR Am J Roentgenol*. 2008;190:1187-1192.
31. Siddiqui MM, Rais-Bahrami S, Turkbey B, et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. *JAMA*. 2015;313:390-397.
32. Baco E, Rud E, Eri LM, et al. A Randomized controlled trial to assess and compare the outcomes of two-core prostate biopsy guided by fused magnetic resonance and transrectal ultrasound images and traditional 12-core systematic biopsy [published online ahead of print April 7, 2015]. *Eur Urol*. doi: 10.1016/j.eururo.2015.03.041.
33. Arsov C, Rabenalt R, Blondin D, et al. Prospective randomized trial comparing magnetic resonance imaging (MRI)-guided in-bore biopsy to MRI-ultrasound fusion and transrectal ultrasound-guided prostate biopsy in patients with prior negative biopsies. *Eur Urol*. 2015;68:713-720.
34. Meng X, Rosenkrantz AB, Mendhiratta N, et al. Relationship between prebiopsy multiparametric magnetic resonance imaging (MRI), biopsy indication, and MRI-ultrasound fusion-targeted prostate biopsy outcomes [published online ahead of print June 22, 2015]. *Eur Urol*. doi: 10.1016/j.eururo.2015.06.005.
35. Rouse P, Shaw G, Ahmed HU, Freeman A, Allen C, Emberton M. Multi-parametric magnetic resonance imaging to rule-in and rule-out clinically important prostate cancer in men at risk: a cohort study. *Urol Int*. 2011;87:49-53.
36. Salami S, Ben-Levi E, Yaskiv O. In patients with a previous negative prostate biopsy and a suspicious lesion on magnetic resonance imaging, is a 12-core biopsy still necessary in addition to a targeted biopsy? *BJU Int*. 2015;115:562-570.
37. Zhang J, Xiu J, Dong Y, et al. Magnetic resonance imaging-directed biopsy improves the prediction of prostate cancer aggressiveness compared with a 12-core transrectal ultrasound-guided prostate biopsy. *Mol Med Rep*. 2014;9:1989-1997.
38. Rosenkrantz AB, Verma S, Turkbey B. Prostate cancer: top places where tumors hide on multiparametric MRI. *AJR Am J Roentgenol*. 2015;204:W449-W456.
39. Volkin D, Turkbey B, Hoang AN, et al. Multiparametric magnetic resonance imaging (MRI) and subsequent MRI/ultrasound fusion-guided biopsy increase the detection of anteriorly located prostate cancers. *BJU Int*. 2014;114:E43-E49.
40. Pepe P, Dibenedetto G, Pennisi M, Fraggetta F, Colecchia M, Aragona F. Detection rate of anterior prostate cancer in 226 patients submitted to initial and repeat transperineal biopsy. *Urol Int*. 2014;93:189-192.
41. Nix JW, Turkbey B, Hoang A, et al. Very distal apical prostate tumours: identification on multiparametric MRI at 3 Tesla. *BJU Int*. 2012;110(11 pt B):E694-E700.
42. Sankineni S, George AK, Brown AM, et al. Posterior subcapsular prostate cancer: Identification with mpMRI and MRI/TRUS fusion-guided biopsy. *Abdom Imaging*. 2015;40:2557-2565.
43. Lawrentschuk N, Haider MA, Daljeet N, et al. "Prostatic evasive anterior tumours": the role of magnetic resonance imaging. *BJU Int*. 2010;105:1231-1236.
44. Brown AM, Elbuluk O, Mertan F, et al. Recent advances in image-guided targeted prostate biopsy. *Abdom Imaging*. 2015;40:1788-1799.
45. Overduin CG, Fütterer JJ, Barentsz JO. MRI-guided biopsy for prostate cancer detection: a systematic review of current clinical results. *Curr Urol Rep*. 2013;14:209-213.
46. Haffner J, Lemaitre L, Puech P, et al. Role of magnetic resonance imaging before initial biopsy: comparison of magnetic resonance imaging-targeted and systematic biopsy for significant prostate cancer detection. *BJU Int*. 2011;108(8 pt 2):E171-E178.
47. Ong WL, Weerakoon M, Huang S, et al. Transperineal biopsy prostate cancer detection in first biopsy and repeat biopsy after negative transrectal ultrasound-guided biopsy: the Victorian Transperineal Biopsy Collaboration experience. *BJU Int*. 2015;116:568-576.
48. Grummet JP, Weerakoon M, Huang S, et al. Sepsis and "superbugs": should we favour the transperineal over the transrectal approach for prostate biopsy? *BJU Int*. 2014;114:384-388.
49. Fütterer JJ, Briganti A, De Visschere P, et al. Can clinically significant prostate cancer be detected with multiparametric magnetic resonance imaging? A systematic review of the literature [published online ahead of print February 2, 2015]. *Eur Urol*. doi: 10.1016/j.eururo.2015.01.013.
50. Itatani R, Namimoto T, Atsuji S, et al. Negative predictive value of multiparametric MRI for prostate cancer detection: outcome of 5-year follow-up in men with negative findings on initial MRI studies. *Eur J Radiol*. 2014;83:1740-1745.
51. Arumainayagam N, Ahmed H, Moore C. Multiparametric MR imaging for detection of clinically significant prostate cancer: a validation cohort study with transperineal template prostate mapping as the reference standard. *Radiology*. 2013;268:761-769.
52. Giannarini G, Zazzara M, Rossanese M, et al. Will multi-parametric magnetic resonance imaging be the future tool to detect clinically significant prostate cancer [serial online]? *Front Oncol*. 2014;4:294.
53. Ouzzane A, Puech P, Villers A. How accurately can MRI detect indolent disease? *Curr Opin Urol*. 2014;24:264-269.
54. De Visschere PJ, Naesens L, Libbrecht L, et al. What kind of prostate cancers do we miss on multiparametric magnetic resonance imaging [published online ahead of print July 3, 2015]? *Eur Radiol*. doi: 10.1007/s00330-015-3894-x.
55. Le JD, Stephenson S, Brugger M, et al. Magnetic resonance imaging-ultrasound fusion biopsy for prediction of final prostate pathology. *J Urol*. 2014;192:1367-1373.
56. Finley DS, Margolis D, Raman SS, et al. Fine-tuning robot-assisted radical prostatectomy planning with MRI. *Urol Oncol*. 2013;31:766-775.
57. Hricak H, Wang L, Wei DC, et al. The role of preoperative endorectal magnetic resonance imaging in the decision regarding whether to preserve or resect neurovascular bundles during radical retropubic prostatectomy. *Cancer*. 2004;100:2655-2663.
58. Park BH, Jeon HG, Jeong BC, et al. Influence of magnetic resonance imaging in the decision to preserve or resect neurovascular bundles at robotic assisted laparoscopic radical prostatectomy. *J Urol*. 2014;192:82-88.
59. Tabatabaei S, Saylor PJ, Coen J, Dahl DM. Prostate cancer imaging: what surgeons, radiation oncologists, and medical oncologists want to know. *AJR Am J Roentgenol*. 2011;196:1263-1266.
60. Shukla-Dave A, Hricak H, Akin O, et al. Preoperative nomograms incorporating magnetic resonance imaging and spectroscopy for prediction of insignificant prostate cancer. *BJU Int*. 2012;109:1315-1322.
61. Rais-Bahrami S, Türkbey B, Rastinehad AR, et al. Natural history of small index lesions suspicious for prostate cancer on multiparametric MRI: recommendations for interval imaging follow-up. *Diagn Interv Radiol*. 2014;20:293-298.
62. Anderson J, Burney S, Brooker JE, et al. Anxiety in the management of localised prostate cancer by active surveillance. *BJU Int*. 2014;114(suppl 1):55-61.
63. Radtke JP, Boxler S, Kuru TH, et al. Improved detection of anterior fibromuscular stroma and transition zone prostate cancer using biparametric and multiparametric MRI with MRI-targeted biopsy and MRI-US fusion guidance. *Prostate Cancer Prostatic Dis*. 2015;18:288-296.

Fusion Pharmaceuticals, Inc.
Exhibit 1024.010

64. Feng TS, Sharif-Afshar AR, Smith SC, et al. Multiparametric magnetic resonance imaging localizes established extracapsular extension of prostate cancer. *Urol Oncol.* 2015;33:109.e15-109.e22.

65. Boesen L, Chabanova E, Løgager V, Balslev I, Mikines K, Thomsen HS. Prostate cancer staging with extracapsular extension risk scoring using multiparametric MRI: a correlation with histopathology. *Eur Radiol.* 2015;25:1776-1785.

66. Gupta RT, Faridi KF, Singh AA, et al. Comparing 3-T multiparametric MRI and the Partin tables to predict organ-confined prostate cancer after radical prostatectomy. *Urol Oncol.* 2014;32:1292-1299.

67. Turkbey B, Pinto PA, Mani H, et al. Prostate cancer: value of multiparametric MR imaging at 3 T for detection–histopathologic correlation. *Radiology.* 2010;255:89-99.

68. Park JJ, Kim CK, Park SY, Park BK, Lee HM, Cho SW. Prostate cancer: role of pretreatment multiparametric 3-T MRI in predicting biochemical recurrence after radical prostatectomy. *AJR Am J Roentgenol.* 2014; 202:W459-W465.

69. Ho R, George A, Frye T, et al. Can mpMRI predict biochemical recurrence after radical prostatectomy? Implications for preoperative staging and surgical planning [abstract]. *J Clin Oncol.* 2015;33(suppl 7). Abstract 161.

70. Lopes Dias J, Lucas R, Magalhães Pina J, et al. Post-treated prostate cancer: normal findings and signs of local relapse on multiparametric magnetic resonance imaging. *Abdom Imaging.* 2015;40:2814-2838.

71. Cha D, Kim CK, Park SY, Park JJ, Park BK. Evaluation of suspected soft tissue lesion in the prostate bed after radical prostatectomy using 3T multiparametric magnetic resonance imaging. *Magn Reson Imaging.* 2015; 33:407-412.

72. Haider MA, Chung P, Sweet J, et al. Dynamic contrast-enhanced magnetic resonance imaging for localization of recurrent prostate cancer after external beam radiotherapy. *Int J Radiat Oncol Biol Phys.* 2008; 70:425-430.

73. Kanthabalan A, Shah T, Arya M, et al. The FORECAST Study—Focal Recurrent Assessment and Salvage Treatment for Radiorecurrent Prostate Cancer [published online ahead of print 2015]. *Contemp Clin Trials*. doi: 10.1016/j.cct.2015.07.004.

74. Parivar F, Hricak H, Shinohara K, et al. Detection of locally recurrent prostate cancer after cryosurgery: evaluation by transrectal magnetic resonance imaging and three-dimensional proton magnetic resonance spectroscopy. *Urology.* 1996;48:594-599.

75. Ahmed HU, Cathcart P, McCartan N, et al. Focal salvage therapy for localized prostate cancer recurrence after external beam radiotherapy: a pilot study. *Cancer.* 2012; 118:4148-4155.

76. Ménard C, Iupati D, Publicover J, et al. MR-guided prostate biopsy for planning of focal salvage after radiation therapy. *Radiology.* 2015;274:181-191.

77. Sundi D, Ross AE, Humphreys EV, et al. African American men with very low-risk prostate cancer exhibit adverse oncologic outcomes after radical prostatectomy: should active surveillance still be an option for them? *J Clin Oncol.* 2013;31:2991-2997.

78. Yamoah K, Deville C, Vapiwala N, et al. African American men with low-grade prostate cancer have increased disease recurrence after prostatectomy compared with Caucasian men. *Urol Oncol.* 2015;33: 70.e15-70.e22.

79. Sundi D, Kryvenko ON, Carter HB, Ross AE, Epstein JI, Schaeffer EM. Pathological examination of radical prostatectomy specimens in men with very low risk disease at biopsy reveals distinct zonal distribution of cancer in black American men. *J Urol.* 2014;191:60-67.

80. Carter BS, Beaty TH, Steinberg GD, Childs B, Walsh PC. Mendelian inheritance of familial prostate cancer. *Proc Natl Acad Sci U S A.* 1992;89:3367-3371.

81. Carter BS, Bova GS, Beaty TH, et al. Hereditary prostate cancer: epidemiologic and clinical features. *J Urol.* 1993;150:797-802.

82. Bock CH, Peyser PA, Gruber SB, Bonnell SE, Tedesco KL, Cooney KA. Prostate cancer early detection practices among men with a family history of disease. *Urology.* 2003;62:470-475.

83. deSouza NM, Morgan VA, Bancroft E, et al. Diffusion-weighted MRI for detecting prostate tumour in men at increased genetic risk [serial online]. *Eur J Radiol Open.* 2014;1:22-27.

84. Abern MR, Bassett MR, Tsivian M, et al. Race is associated with discontinuation of active surveillance of low-risk prostate cancer: results from the Duke Prostate Center. *Prostate Cancer Prostatic Dis.* 2013;16:85-90.

85. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin.* 2015;65:5-29.

86. National Cancer Institute. Cancer Health Disparities. Bethesda, MD: National Cancer Institute; 2015. cancer.gov/. Accessed April 1, 2015.

87. Hoffman RM, Gilliland FD, Eley JW, et al. Racial and ethnic differences in advanced-stage prostate cancer: the Prostate Cancer Outcomes Study. *J Natl Cancer Inst.* 2001; 93:388-395.

88. Hambrock T, Somford DM, Huisman HJ, et al. Relationship between apparent diffusion coefficients at 3.0-T MR imaging and Gleason grade in peripheral zone prostate cancer. *Radiology.* 2011;259:453-461.

89. Vargas HA, Akin O, Franiel T, et al. Diffusion-weighted endorectal MR imaging at 3 T for prostate cancer: tumor detection and assessment of aggressiveness. *Radiology.* 2011;259:775-784.

90. Sankineni S, Wood BJ, Rais-Bahrami S, et al. Image-guided focal therapy for prostate cancer. *Diagn Interv Radiol.* 2014;20:492-497.

91. Le Nobin J, Rosenkrantz AV, Villers A, et al. Image guided focal therapy for magnetic resonance imaging visible prostate cancer: defining a 3-dimensional treatment margin based on magnetic resonance imaging histology co-registration analysis. *J Urol.* 2015;194:364-370.

92. Polascik TJ. Focal therapy of prostate cancer: making steady progress toward a first-line image-guided treatment modality. *Curr Opin Urol.* 2015;25:183-184.

93. Oto A, Sethi I, Karczmar G, et al. MR imaging-guided focal laser ablation for prostate cancer: phase I trial. *Radiology.* 2013;267:932-940.

94. Lee T, Mendhiratta N, Sperling D, Lepor H. Focal laser ablation for localized prostate cancer: principles, clinical trials, and our initial experience. *Rev Urol.* 2014;16:55-66.

95. Lepor H, Llukani E, Sperling D, Futterer JJ. Complications, recovery, and early functional outcomes and oncologic control following in-bore focal laser ablation of prostate cancer [published online ahead of print 2015]. *Eur Urol.* doi: 10.1016/j.eururo.2015.04.029.

96. Valerio M, Stricker PD, Ahmed HU, et al. Initial assessment of safety and clinical feasibility of irreversible electroporation in the focal treatment of prostate cancer. *Prostate Cancer Prostatic Dis.* 2014;17:343-347.

97. Davalos RV, Bhonsle S, Neal RE 2nd. Implications and considerations of thermal effects when applying irreversible electroporation tissue ablation therapy. *Prostate.* 2015;75:1114-1118.

Fusion Pharmaceuticals, Inc.
Exhibit 1024.011