REVIEWS IN UROLOGY

Contemporary Approaches to Diagnosing Prostate Cancer

Ashley E. Ross, MD, PhD[1]; Alon Lazarovich, MD, MPH[2]; Aaron S. Dahmen, MD[2]; Abhinav Sidana, MD, MPH[2]; Jack Millot, BA[3]; Jonathan E. Shoag, MD[3]; Hangcheng Fu, MD[4]; John Eifler, MD[4,5]

[1]Department of Urology, Northwestern Feinberg School of Medicine, Chicago, Illinois
[2]Section of Urology, Department of Surgery, University of Chicago Pritzker School of Medicine, Chicago, Illinois
[3]Department of Urology, University Hospitals Cleveland Medical Center, Case Western Reserve University School of Medicine, Cleveland, Ohio
[4]Department of Urology, University of Louisville School of Medicine, Louisville, Kentucky
[5]First Urology PSC, Louisville, Kentucky

KEYWORDS:
Prostatic neoplasms; biomarkers; magnetic resonance imaging

Contemporary Approaches: An Overview by Dr Ross

The diagnosis of prostate cancer (PCa) has changed substantially over the last decade. An increased understanding of disease behavior has led to the development of more specific biomarkers that may limit the numbers of prostate biopsies performed as well as the overdiagnosis of low-grade disease. We have concurrently seen the refinement of imaging techniques such as multiparametric magnetic resonance imaging (mpMRI), which can also limit overdiagnosis and aid in the discovery of clinically significant disease. We now have various options for performing ultrasound-guided biopsies, including transperineal and transrectal approaches. In this article, we gather perspectives on contemporary pathways toward the diagnosis of PCa from experts practicing in large urology practice groups and academia.

Where Are We in 2024? Drs Lazarovich, Dahmen, and Sidana Weigh In

Prostate cancer diagnosis has witnessed remarkable advancements in recent years, ushering in a new era of precision and effectiveness. One noteworthy stride in PCa diagnosis is the revolution sparked by mpMRI.[1,2] Over the past decade, mpMRI has emerged as a game changer, providing detailed images that enable clinicians to better detect and characterize cancerous lesions and to improve the risk stratification of PCa.[3] The use of mpMRI has improved the diagnosis rate of clinically significant PCa (csPCa) and lowered the diagnosis rate of non-csPCa,[4,5] reducing unnecessary biopsies and mitigating the harmful impact on quality of life as a result of overtreatment.

Citation: Ross AE, Lazarovich A, Dahmen AS, et al. Contemporary approaches to diagnosing prostate cancer. *Rev Urol.* 2024;23(1):e37-e41.

Corresponding author: Ashley E. Ross, MD, PhD, Northwestern Memorial Hospital, Arkes Bldg 2300, 676 N St Claire St, Chicago, IL 60611 (ashley.ross1@northwestern.edu)

In tandem with the mpMRI revolution, the advent of PCa biomarkers has added another layer of sophistication to the diagnostic process. The combination of mpMRI with prostate-specific antigen (PSA) density and other biomarkers has proven to be a valuable set of prognostic factors.[6] Genomic testing, including platforms such as Decipher (Veracyte Labs SD), Prolaris (Myriad Genetics, Inc), and Oncotype DX (Exact Sciences Corporation),[7] supports patient management decisions by helping make the choice between active surveillance and active treatment. Emerging biomarkers such as the Stockholm biomarker also promise to enhance diagnostic power by potentially addressing gaps and obstacles associated with PSA screening.[8]

Over the past few years, biopsy techniques have undergone a paradigm shift, first with the wide adoption of mpMRI-guided fusion biopsies and more recently with the transperineal approach, which has gained prominence both as an "in-office" and as an "operating room" procedure. The transperineal approach has been demonstrated to have comparable cancer detection to transrectal biopsy, with the theoretical advantage of lower risk of infectious complications. Two recently published randomized trials showed no significant difference in infections between the 2 approaches, although transperineal biopsies being performed without periprocedural routine antibiotics highlights the approach's lower risk of bacterial seeding.[9,10]

Contemporary PCa diagnosis has undergone a seismic shift over the past decade. The integration of mpMRI, biomarkers, and fusion biopsy has enhanced diagnostic accuracy and risk stratification and has empowered patients and clinicians by giving them a more informed and personalized approach to treatment, such as PCa focal therapy.[11] Moreover, the transperineal approach to prostate biopsy has the potential to minimize morbidity from infectious complications without excessive antibiotic use and to promote antibiotic stewardship in the process.

ABBREVIATIONS

csPCa	clinically significant prostate cancer
GG	Grade Group
mpMRI	multiparametric magnetic resonance imaging
PCa	prostate cancer
PI-RADS	Prostate Imaging Reporting and Data System
PSA	prostate-specific antigen

PCa Diagnosis Today: Dr Millot and Shoag

My practice on the East Side of Cleveland consists of a racially and ethnically diverse population, with a considerable number of patients who may be at higher risk for PCa mortality. Prostate cancer diagnosis begins with an elevated, age-adjusted PSA measurement. We do not routinely perform digital rectal examination based on existing data from large, randomized studies (the Prostate, Lung, Colorectal, and Ovarian Cancer Screen Trial; PROBASE; and GÖTEBORG-2 trials), which have not shown a benefit to digital rectal examination, particularly when using MRI.[12-14] Patients with an elevated, age-adjusted PSA level will generally undergo a 4Kscore test. Some data suggest that using 4Kscore before MRI optimizes tradeoffs in that use of MRI in patients with a low (<5%) or substantially elevated (>23%) 4Kscore does not influence their risk of csPCa at biopsy.[15] We use the 4Kscore because of its considerable validation in the United States, including in African American populations, and because we have not had issues with patients incurring out-of-pocket expenses with the test.[16,17] In patients with more than 1 elevated PSA screening result, we order a 4Kscore test and MRI concurrently. The rationale for both triage tests is that the 4Kscore test serves as a safety net for potentially aggressive lesions that are invisible on MRI scans, an approach analogous to ongoing randomized trial protocols.[18] Though the manufacturer recommends a 4Kscore threshold of at least 7.5% (probability of having aggressive disease), we

communicate results as a risk continuum; if a patient has a negative MRI finding, biopsy is frequently avoided above this threshold.

Patients with an elevated 4Kscore or with Prostate Imaging Reporting and Data System (PI-RADS) level 4 or 5 lesions as well as many patients with PI-RADS 3 lesions on MRI scans (depending on their risk tolerance and other factors) will undergo prostate biopsy. These biopsies are generally done transperineally with anesthesia in an ambulatory setting. Both systematic biopsies (a modified Barzell template of 20 core samples) and targeted biopsies (5-6 cores per lesion) are performed. We perform our transperineal biopsies with propofol (but no laryngeal mask airway or endotracheal tube), local anesthesia (Marcaine; Pfizer), and intravenous ketorolac tromethamine. We believe that anesthesia improves patient comfort. Although in-office biopsies are generally tolerated, the biopsy experience can be negative for some patients. Our practice is structured to efficiently perform more than 10 biopsies with anesthesia in a morning. We avoid biopsy of the transition zone and bladder neck to minimize the risk of retention, assuming that there are no MRI-revealed lesions in these locations. In our experience, biopsy retention rates are below 1%, and with the transperineal approach using anesthesia, we find no downside to comprehensive sampling. Despite the lower risk of infection with transperineal biopsy than with transrectal biopsy, we give antibiotic prophylaxis (ceftriaxone) because the risk of infection is still present (particularly for patients with a history of urinary tract infections or bladder stones), and in our experience, with antibiotics, the risk of infection approaches approximately 1 in 1000 biopsies.

For most patients with a negative biopsy, we refer them back to their primary care practitioner for routine PSA screenings, given the low likelihood of disease and our extensive sampling. For patients with Grade Group 1 (GG1) disease and for many patients with GG2 disease, we generally recommend surveillance. Notable exceptions include patients with GG1 disease and a PI-RADS 5 lesion, whom studies show are at risk of progression to GG3 or higher disease on surveillance, as well as patients with cribriform or intraductal patterns on histology, for whom European Association of Urology guidelines recommend treatment.[19,20]

An Integrative Approach With Biomarkers, MRI, and Biopsy Techniques: Drs Fu and Eifler

Despite ongoing debates surrounding overdiagnosis and unnecessary biopsies, PSA remains the most widely used biomarker for the diagnosis of PCa. No biomarker has yet supplanted PSA, though novel tests, such as SelectMDx (MDxHealth), ExoDx (Bio-Techne), and the Prostate Health Index, may be employed adjunctively to reduce biopsy frequency. Studies indicate that increased adoption of biomarker testing could potentially avert 26% to 33% of prostate biopsies, with a low risk of missed diagnoses (3%-7%).[21] Data from prospective trials are necessary, however, to determine the most beneficial clinical scenarios in which to use biomarkers. In our practice, these PSA adjuncts are used sparingly. In certain clinical conditions, such as in patients with elevated PSA values and ambivalent MRI results, such tests may be used as a tiebreaker.

Multiparametric MRI of the prostate has become an important tool in PCa diagnosis and surgical planning. Magnetic resonance imaging fusion biopsy techniques have a 30% higher detection rate for csPCa than traditional systematic biopsy.[22,23] The improvement in PCa localization has allowed the development of focal therapy for PCa, as well. In addition to MRI, emerging techniques—such as robot-assisted, in-bore, MRI-targeted biopsy and integrated MRI/positron emission tomography–computed tomography fusion biopsy with prostate-specific membrane antigen radiolabeled with ^{68}Ga—might further enhance detection rates,[24,25] though clinical evidence of their superiority remains limited. Though the improvement in accuracy yielded by MRI scans may guide clinical decision-making, it should be noted that prostate MRI remains expensive and has not demonstrated improvement in survival outcomes. Long wait times for prostate MRI may raise patient anxiety at an

already-stressful time. In our practice, the decision to pursue MRI before initial prostate biopsy is therefore individualized based on shared decision-making. For patients undergoing a second biopsy, such as patients on active surveillance or patients with prior negative biopsies, most will have undergone prostate MRI.

Once the decision has been made to pursue biopsy, the next decision is whether to pursue a transperineal or a transrectal approach. Empirically, transperineal biopsy is associated with increased discomfort but fewer infections compared with transrectal approaches. A systematic review indicated a higher detection rate of csPCa per patient and per lesion in MRI-guided transperineal biopsies than in MRI-guided transrectal biopsies.[26] Recent randomized controlled trials, such as the ProBE-PC and PREVENT trials, have investigated biopsy-associated complications.[9,10] The ProBE-PC trial found no significant differences in overall complication rates, infection rates, or urinary retention rates between the transrectal and transperineal groups. The PREVENT trial also reported no significant differences in infectious rates between transperineal and transrectal biopsies. With infection rates of 1% to 2%, respectively, at baseline, however, the trials were underpowered to detect small differences in infection rates. In our practice, initial biopsy is typically transrectal, though patients undergoing a second biopsy will usually undergo a transperineal biopsy.

In summary, contemporary PCa diagnosis is characterized by a nuanced integration of PSA testing, advanced biomarkers, MRI technologies, and both transrectal and transperineal biopsy methods. Ongoing research seeks to optimize accuracy, patient comfort, and cost-effectiveness.

Article Information

Published: March 31, 2024.

Conflict of Interest Disclosures: None.

Funding/Support: None.

Author Contributions: All authors participated equally in content creation and writing.

Data Availability Statement: None.

References

1. Turkbey B, Brown AM, Sankineni S, Wood BJ, Pinto PA, Choyke PL. Multiparametric prostate magnetic resonance imaging in the evaluation of prostate cancer. *CA Cancer J Clin.* 2016;66(4):326-336. doi:10.3322/caac.21333
2. Kasson M, Ortman M, Gaitonde K, Verma S, Sidana A. Imaging prostate cancer using multiparametric magnetic resonance imaging: past, present, and future. *Semin Roentgenol.* 2018;53(3):200-205. doi:10.1053/j.ro.2018.04.008
3. Turkbey B, Rosenkrantz AB, Haider MA, et al. Prostate Imaging Reporting and Data System version 2.1: 2019 update of Prostate Imaging Reporting and Data System version 2. *Eur Urol.* 2019;76(3):340-351. doi:10.1016/j.eururo.2019.02.033
4. Kasivisvanathan V, Rannikko AS, Borghi M, et al; PRECISION Study Group Collaborators. MRI-targeted or standard biopsy for prostate-cancer diagnosis. *N Engl J Med.* 2018;378(19):1767-1777. doi:10.1056/NEJMoa1801993
5. Ahmed HU, El-Shater Bosaily A, Brown LC, et al; PROMIS study group. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *Lancet.* 2017;389(10071):815-822. doi:10.1016/S0140-6736(16)32401-1
6. Cash H, Schostak M. The role of PSA density in the MRI pathway for prostate cancer diagnostics. *Prostate Cancer Prostatic Dis.* 2023;26(3):437-438. doi:10.1038/s41391-022-00579-6
7. Brooks MA, Thomas L, Magi-Galluzzi C, et al. GPS assay association with long-term cancer outcomes: twenty-year risk of distant metastasis and prostate cancer–specific mortality. *JCO Precis Oncol.* 2021:5:PO.20.00325. doi:10.1200/PO.20.00325
8. Nordström T, Discacciati A, Bergman M, et al; STHLM3 study group. Prostate cancer screening using a combination of risk-prediction, MRI, and targeted prostate biopsies (STHLM3-MRI): a prospective, population-based, randomised, open-label, non-inferiority trial. *Lancet Oncol.* 2021;22(9):1240-1249. doi:10.1016/S1470-2045(21)00348-X
9. Hu JC, Assel M, Allaf ME, et al. Transperineal versus transrectal magnetic resonance imaging–targeted and systematic prostate biopsy to prevent infectious complications: the PREVENT randomized trial. *Eur Urol.* 2024:S0302-2838(23)03342-0. doi:10.1016/j.eururo.2023.12.015
10. Mian BM, Feustel PJ, Aziz A, et al. Complications following transrectal and transperineal prostate biopsy: results of the ProBE-PC randomized clinical trial. *J Urol.* 2024;211(2):205-213. doi:10.1097/JU.0000000000003788
11. Calio B, Kasson M, Sugano D, et al. Multiparametric MRI: an opportunity for focal therapy of prostate cancer. *Semin Roentgenol.* 2018;53(3):227-233. doi:10.1053/j.ro.2018.04.007
12. Halpern JA, Shoag JE, Mittal S, et al. Prognostic significance of digital rectal examination and prostate specific antigen in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening arm. *J Urol.* 2017;197(2):363-368. doi:10.1016/j.juro.2016.08.092
13. Hugosson J, Månsson M, Wallström J, et al; GÖTESBORG-2 Trial Investigators. Prostate cancer screening with PSA

and MRI followed by targeted biopsy only. *N Engl J Med.* 2022;387(23):2126-2137. doi:10.1056/nejmoa2209454

14. Arsov C, Albers P, Herkommer K, et al. A randomized trial of risk-adapted screening for prostate cancer in young men—results of the first screening round of the PROBASE trial. *Int J Cancer.* 2022;150(11):1861-1869. doi:10.1002/ijc.33940
15. Marzouk K, Ehdaie B, Vertosick E, Zappala S, Vickers A. Developing an effective strategy to improve the detection of significant prostate cancer by combining the 4Kscore and multiparametric MRI. *Urol Oncol.* 2019;37(10):672-677. doi:10.1016/j.urolonc.2019.07.010
16. Punnen S, Freedland SJ, Polascik TJ, et al. A multi-institutional prospective trial confirms noninvasive blood test maintains predictive value in African American men. *J Urol.* 2018;199(6):1459-1463. doi:10.1016/j.juro.2017.11.113
17. Parekh DJ, Punnen S, Sjoberg DD, et al. A multi-institutional prospective trial in the USA confirms that the 4Kscore accurately identifies men with high-grade prostate cancer. *Eur Urol.* 2015;68(3):464-470. doi:10.1016/j.eururo.2014.10.021
18. Eklund M, Jäderling F, Discacciati A, et al; STHLM3 consortium. MRI-targeted or standard biopsy in prostate cancer screening. *N Engl J Med.* 2021;385(10):908-920. doi:10.1056/NEJMoa2100852
19. Wang AZ, O'Conno LP, Yerram NK, et al. PI-RADS® category as a predictor of progression to unfavorable risk prostate cancer in men on active surveillance. *J Urol.* 2020;204(6):1229-1235. doi:10.1097/JU.0000000000001307
20. Mottet N, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer—2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol.* 2021;79(2):243-262. doi:10.1016/j.eururo.2020.09.042
21. Eyrich NW, Morgan TM, Tosoian JJ. Biomarkers for detection of clinically significant prostate cancer: contemporary clinical data and future directions. *Transl Androl Urol*. 2021;10(7):3091-3103. doi:10.21037/tau-20-1151
22. 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(4):390-397. doi:10.1001/jama.2014.17942
23. Izadpanahi MH, Elahian A, Gholipour F, et al. Diagnostic yield of fusion magnetic resonance-guided prostate biopsy versus cognitive-guided biopsy in biopsy-naive patients: a head-to-head randomized controlled trial. *Prostate Cancer Prostatic Dis*. 2021;24(4):1103-1109. doi:10.1038/s41391-021-00366-9
24. Donato P, Morton A, Yaxley J, et al. ^{68}Ga-PSMA PET/CT better characterises localised prostate cancer after MRI and transperineal prostate biopsy: is ^{68}Ga-PSMA PET/CT guided biopsy the future? *Eur J Nucl Med Mol Imaging*. 2020;47(8):1843-1851. doi:10.1007/s00259-019-04620-0
25. Ferraro DA, Becker AS, Kranzbühler B, et al. Diagnostic performance of ^{68}Ga-PSMA-11 PET/MRI-guided biopsy in patients with suspected prostate cancer: a prospective single-center study. *Eur J Nucl Med Mol Imaging*. 2021;48(10):3315-3324. doi:10.1007/s00259-021-05261-y
26. Rai BP, Mayerhofer C, Somani BK, Kallidonis P, Nagele U, Tokas T. Magnetic resonance imaging/ultrasound fusion-guided transperineal versus magnetic resonance imaging/ultrasound fusion-guided transrectal prostate biopsy—a systematic review. *Eur Urol Oncol*. 2021;4(6):904-913. doi:10.1016/j.euo.2020.12.012