

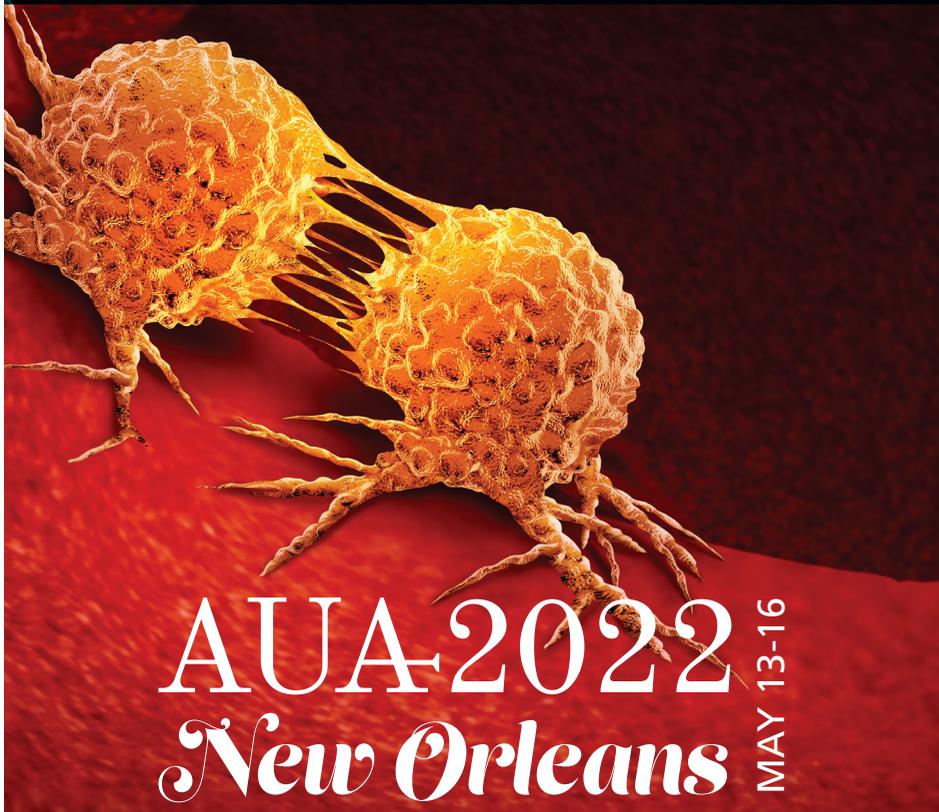


American  
Urological  
Association

# AUA News

THE OFFICIAL NEWSMAGAZINE OF THE AMERICAN UROLOGICAL ASSOCIATION

## 2022 AUA Annual Meeting Highlights: Prostate Cancer



AUA 2022  
*New Orleans* MAY 13-16

Features highlights from the following AUA 2022 Annual Meeting sessions:

- Prostate Cancer Update 2022
- Localized Prostate Cancer: AUA/ASTRO Guideline 2022
- AUA Guidelines on Advanced Prostate Cancer
- The Changing Face of Advanced Prostate Cancer 2022
- Genetic Testing in Prostate Cancer: Understanding Clinical Implications for Early Detection and Management of Localized and Advanced Disease
- Incorporating Genomic Testing for Prostate Cancer into Your Practice
- Urological Care for the Advanced Practice Provider Program. Prostate Cancer Biomarkers: What to Choose and When to Use

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Incorporating Genomic Testing for Prostate Cancer into Your Practice

Urological Care for the Advanced Practice Provider Program. Prostate Cancer Biomarkers: What to Choose and When to Use

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## AUA2022 COURSE

## Prostate Cancer Update 2022

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## Learning Objective

*At the conclusion of the activity, participants will be able to explain the research and clinical publications from the past year on prostate cancer concerning risk stratification, screening, and biopsy methods.*

## Statistics and Epidemiology

During the PSA screening era, the incidence of metastatic prostate cancer decreased strikingly (4%-5% presented with metastases) and the prostate cancer-specific mortality rate decreased by 53%.<sup>1</sup> Currently, 71%-73% of new cases present with clinically localized disease, with a 5-year survival rate of 96%-98%.<sup>2</sup> Following the 2012 USPSTF (U.S. Preventive Services Task Force) grade D recommendation against prostate cancer screening, in men younger than 70 years old, PSA screening, biopsy, and overall prostate cancer detection rates significantly decreased, while the rates of metastatic disease significantly increased in all races and age groups.<sup>3,4</sup> After the USPSTF's 2018 upgrade to grade C, there has been an increase in PSA testing across all age groups—ironically, mostly in men aged 70-89 years.<sup>5</sup> In young Black men, PSA screening was associated with a lower rate of metastases and prostate cancer mortality.<sup>6</sup> Older adults' ingrained beliefs about screening may run counter to guideline concepts.<sup>7</sup> The higher Gleason scores in older men

should be considered when counseling patients.<sup>8</sup> Some are suggesting that Gleason grade group (GG) 1 should not be called “cancer;” however, most prostate cancer deaths occur in men initially diagnosed with low-grade disease.<sup>9</sup>

Socioeconomic status accounts for most racial prostate cancer mortality disparities.<sup>10-12</sup> Black men who receive primary definitive treatment have a lower risk of metastases.<sup>13</sup> Online information about prostate cancer lacks racial and ethnic diversity.<sup>14</sup>

More plant-based consumption and physical activity are associated with a lower risk of elevated PSA<sup>15</sup> and fatal prostate cancer.<sup>16</sup> Statin use does not compromise PSA screening.<sup>17</sup> Nonselective beta-blocker use at the time of radical prostatectomy is associated with less treatment for prostate cancer recurrence.<sup>18</sup>

## Risk Stratification, Screening, and Biopsy

An artificial intelligence platform was able to detect, grade, and quantify prostate cancer with high accuracy and less interobserver variability.<sup>19</sup> MRI and genomic testing have increased the proportion of patients receiving observation.<sup>20</sup> Altered DNA damage response is an important mechanism for aggressive prostate cancer in men of all races.<sup>21</sup> The most important germline variants are pathogenic mutations of *BRCA2*. Lynch syndrome predisposes to various cancers, and *MSH2* and *MSH6* carriers have a higher prostate cancer incidence and more clinically significant disease.<sup>22</sup> Common genetic variants individually conferring little risk for prostate cancer but combined in a “polygenic score” can confer substantial risk for prostate cancer, including aggressive disease, across ancestry groups<sup>23</sup> and can help further stratify the risks due to *BRCA1/2* mutations.<sup>24</sup>

MRI-targeted plus systematic biopsies detect more significant and less insignificant prostate cancer.<sup>24-28</sup> Multiparametric ultrasonography (an of-

fice procedure) compares favorably to MRI;<sup>29</sup> however, both miss some cancers detected by the other. Risk calculators provide additional information.<sup>28</sup> MRI-targeted transperineal biopsy plus systematic biopsies reduce infections (even without antibiotics) and may be advantageous for sampling anterior and apical lesions.<sup>30</sup> 68-Ga prostate-specific membrane antigen (PSMA) positron emission tomography (PET) has a sensitivity of 40% and specificity of 95% for pelvic node metastasis in intermediate- and high-risk prostate cancer.<sup>31</sup>

## Active Surveillance

Active surveillance rates are lower in the U.S. than in England.<sup>32</sup> A 22-feature genomic classifier plus clinical variables outperformed the clinical model and correlated with biopsy upgrading on active surveillance.<sup>33</sup> This classifier provides independent prognostic value in all studies and settings with improved discrimination.<sup>34</sup> Men who had annual surveillance biopsies are more likely to be treated, with no difference in upgrading. Frequent biopsies may deter some men from continuing active surveillance despite their having no evidence of tumor progression.<sup>35</sup> In active surveillance, a confirmatory biopsy should be performed within 1 year. Men with a negative MRI or negative surveillance biopsies remain on surveillance longer. Older men require closer monitoring.<sup>36</sup> PSA density is important in discriminating the risk of upgrade among men on active surveillance with a negative MRI scan.<sup>37</sup> Most active surveillance patients eventually undergo delayed treatment, depending considerably on sociodemographic factors.<sup>38,39</sup> Active surveillance is increasing for low- to intermediate-risk disease. A comparison of GG1 and GG2 patients found no difference in reclassification, but GG2 patients had more treatment without reclassification, and

→ Continued on page 4

there was no difference in biochemical recurrence at 3 years.<sup>40</sup>

## Radical Prostatectomy

An evaluation of surgeon radical prostatectomy volume and postoperative potency ranged from 3% to 44% at 24-month follow-up with no correlation with case volume.<sup>41</sup> Treatment-related regret is greater after prostatectomy than for surveillance or radiotherapy, and is strongly tied to expectations of efficacy and side effects.<sup>42</sup> In patients with nodal invasion and PSA persistence after prostatectomy, the 5- and 10-year prostate cancer-specific survival probabilities are 89% and 68%, respectively.<sup>43</sup> The low sensitivity of PSMA PET scans for lymph node metastases (~40%) argues for lymphadenectomy or treating the pelvic nodes with radiotherapy in men at high risk for involvement.

## Focal Therapy

A meta-analysis of focal therapies suggests that photodynamic therapy and high-intensity focused ultrasound are the most promising and are well tolerated; however, long-term data are lacking.

## Radiotherapy

Black men enrolled in randomized clinical trials present with more aggressive disease but have better outcomes with definitive radiotherapy.<sup>44</sup> A hydrogel implant may be placed between the prostate and rectum to reduce the risk of post-radiotherapy rectal complications, but the clinical differences are marginal. An analysis of a randomized trial comparing 3 different radiotherapy fractionation schemes showed similar outcomes with no difference by risk category.

For men undergoing radiotherapy, erectile dysfunction was worse and hot flashes were more frequent with luteinizing hormone-releasing hormone (LHRH) agonist, while breast symptoms were more common with the antiandrogen.<sup>45</sup> A prospective comparison of radiotherapy with dual agent androgen-deprivation therapy (ADT) with bicalutamide plus either an LHRH agonist or a 5 $\alpha$ -reductase inhibitor (5ARI) revealed more breast symptoms but better sexual function in the 5ARI

group. Biochemical outcomes did not appear compromised with 5ARI use.

The patterns of recurrence as defined by a Ga-PSMA PET scan in men with biochemical failure after radiotherapy revealed that 91% of scans showed uptake, and 57% were felt to be amenable to salvage therapy.<sup>46</sup> Brachytherapy is an option for men with isolated local recurrence after radiotherapy. With a follow-up of 6.7 years, freedom from recurrence was 68% at 5 years and 46% at 10 years, and the 10-year overall survival was 70%. Subsequent local failure was rare, and 19% developed distant metastases (this study previously reported a grade 3 rate of late gastrointestinal or genitourinary toxicity of ~15%).<sup>47</sup> Hematuria after salvage radiotherapy occurred in 45% of patients at 8 years of follow-up, and 15% required intervention beyond cystoscopy. Most cases were self-limited, although 31% had recurrent episodes.<sup>48</sup>

## Advanced Disease

ADT is not associated with decreased mortality from SARS-CoV-2 infection.<sup>49</sup> Abiraterone plus a glucocorticoid (Abi/Pred) and 2 years of ADT is a new standard treatment for men with localized high-risk prostate cancer receiving radiotherapy.<sup>50</sup> A prospective, randomized study of cardiovascular risk with degarelix vs leuprolide for 1 year revealed no difference in cardiovascular outcomes.<sup>51</sup> Apalutamide plus Abi/Pred delays time to PSA rise during the off-period of intermittent ADT.<sup>52</sup> Docetaxel plus ADT with an LHRH agonist or antagonist should be further intensified with darolutamide in metastatic hormone-sensitive prostate cancer.<sup>53</sup> Black men have improved overall survival with Abi/Pred.<sup>54</sup> Cabazitaxel is superior to treatment with a second androgen receptor inhibitor.<sup>55</sup>

In patients with metastatic castrate-resistant prostate cancer (mCRPC), if the tumor cells express PSMA on their surfaces, Lu177-PSMA-617 may be a more effective therapy than switching to another hormonal therapy or to cabazitaxel (65% vs 37% PSA-response rate). Dual inhibition of the Akt serine/threonine kinase family (AKT) and the androgen receptor can modestly improve outcomes. Further studies ongoing with AKT inhib-

itors need to have the *P10* status or the tumor determined ahead of time. Patients should have their primary or metastatic tumor sequenced.<sup>55</sup> Bipolar androgen therapy may resensitize mCRPC to ADT, and there is an advantage to using bipolar androgen therapy first.<sup>56</sup>

Immunotherapy with atezolizumab<sup>57</sup> or an autologous dendritic cell-based vaccine is unlikely to work in unselected mCRPC patients.<sup>58</sup> Atezolizumab may work if there is an immune signature in the tumor (occurs rarely); however, it may work in Lynch syndrome patients.<sup>57</sup>

There is a population of androgen-independent cells in the prostatectomy specimen.<sup>59</sup> Genomic sequencing of the primary tumor usually is concordant with cell-free DNA or metastatic sample and may provide useful information, eg for Lynch, *P10* loss, or *AKT* variants, ie it might have therapeutic implications. ■

1. Surveillance, Epidemiology, and End Results Program. Prostate: long-term trends in U.S. age-adjusted mortality rates, 1975-2019. National Cancer Institute; 2022. Accessed March 24, 2022. [https://seer.cancer.gov/explorer/application.html?site=66&data\\_type=2&graph\\_type=1&compareBy=race&chk\\_race\\_1=1&hdn\\_sex=2&age\\_range=1&advopt\\_precision=1&advopt\\_show\\_ci=on&advopt\\_display=2](https://seer.cancer.gov/explorer/application.html?site=66&data_type=2&graph_type=1&compareBy=race&chk_race_1=1&hdn_sex=2&age_range=1&advopt_precision=1&advopt_show_ci=on&advopt_display=2).
2. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin.* 2022;72(1):7-33.
3. Desai MM, Cacciamani GE, Gill K, et al. Trends in incidence of metastatic prostate cancer in the US. *JAMA Netw Open.* 2022;5(3):e222246.
4. Horton B, Alexeff S, Prausnitz S, Avins AL, Presti J. Race-specific trends in prostate cancer screening and presentation before and after the 2012 United States Preventive Services Task Force statement. *Urol Pract.* 2022;9(1):64-71.
5. Leapman MS, Wang R, Park H, et al. Changes in prostate-specific antigen testing relative to the revised US Preventive Services Task Force recommendation on prostate cancer screening. *JAMA Oncol.* 2022;8(1):41-47.
6. Qiao EM, Lynch JA, Lee KM, et al. Evaluating prostate-specific antigen screening for young African American men with cancer. *J Natl Cancer Inst.* 2022;114(4):592-599.
7. Smith J, Dodd RH, Gainey KM, et al. Patient-reported factors associated with older adults' cancer screening decision-making: a systematic review. *JAMA Netw Open.* 2021;4(11):e2133406.
8. Godtman RA, Kollberg KS, Pihl CG, Månsson M, Hugoson J. The association between age, prostate cancer risk, and higher Gleason score in a long-term screening program: results from the Göteborg-1 Prostate Cancer Screening Trial. *Eur Urol.* 2022; doi: 10.1016/j.eururo.2022.01.018.
9. Clark R, Narod S. Patterns of mortality after prostate cancer: a SEER-based analysis. Presented at annual meeting of the Society of Urologic Oncology, Orlando, Florida, December 1-3, 2021.
10. Cheng E, Soulos PR, Irwin ML, et al. Neighborhood and individual socioeconomic disadvantage

- and survival among patients with nonmetastatic common cancers. *JAMA Netw Open.* 2021;4(12):e2139593.
11. Leapman MS, Dinan M, Pasha S, et al. Mediators of racial disparity in the use of prostate magnetic resonance imaging among patients with prostate cancer. *JAMA Oncol.* 2022;8(5):687-696.
  12. Stern N, Ly TL, Welk B, et al. Association of race and ethnicity with prostate cancer-specific mortality in Canada. *JAMA Netw Open.* 2021;4(12):e2136364.
  13. Yamoah K, Lee KM, Awasthi S, et al. Racial and ethnic disparities in prostate cancer outcomes in the Veterans Affairs Health Care System. *JAMA Netw Open.* 2022;5(1):e2144027.
  14. Loeb S, Borno HT, Gomez S, et al. Representation in online prostate cancer content lacks racial and ethnic diversity: implications for Black and Latinx Men. *J Urol.* 2022;207(3):559-564.
  15. Mouzannar A, Kuchakulla M, Blachman-Braun R, et al. Impact of plant-based diet on PSA level: data from the National Health and Nutrition Examination Survey. *Urology.* 2021;156:205-210.
  16. Loeb S, Fu BC, Bauer SR, et al. Association of plant-based diet index with prostate cancer risk. *Am J Clin Nutr.* 2022;115(3):662-670.
  17. Vetterranta A, Murtola TJ, Raitanen J, et al. Outcomes of Screening for Prostate Cancer Among Men Who Use Statins. *JAMA Oncol.* 2022;8(1):61-68.
  18. Sivanesan S, Tasken KA, Grytli HH. Association of beta-blocker use at time of radical prostatectomy with rate of treatment for prostate cancer recurrence. *JAMA Netw Open.* 2022;5(1):e2145230.
  19. Huang W, Randhawa R, Jain P, et al. Development and validation of an artificial intelligence-powered platform for prostate cancer grading and quantification. *JAMA Netw Open.* 2021;4(11):e2132554.
  20. Leapman MS, Wang R, Park HS, et al. Adoption of new risk stratification technologies within US hospital referral regions and association with prostate cancer management. *JAMA Netw Open.* 2021;4(10):e2128646.
  21. Plym A, Diossy M, Szallasi Z, et al. DNA repair pathways and their association with lethal prostate cancer in African American and European American men. *JNCI Cancer Spectr.* 2022;6(1):pkab097.
  22. Bancroft EK, Page EC, Brook MN, et al. A prospective prostate cancer screening programme for men with pathogenic variants in mismatch repair genes (IMPACT): initial results from an international prospective study. *Lancet Oncol.* 2021;22(11):1618-1631.
  23. Pagadala MS, Lynch J, Karunamuni R, et al. Polygenic risk of any, metastatic, and fatal prostate cancer in the Million Veteran Program. Accessed April 15, 2022. <https://www.medrxiv.org/content/10.1101/2021.09.24.21264093v4.full.pdf>.
  24. Barnes DR, Silvestri V, Leslie G, et al. Breast and prostate cancer risks for male BRCA1 and BRCA2 pathogenic variant carriers using polygenic risk scores. *J Natl Cancer Inst.* 2022;114(1):109-122.
  25. Eklund M, Jaderling F, Discacciati A, et al. MRI-targeted or standard biopsy in prostate cancer screening. *N Engl J Med.* 2021;385(10):908-920.
  26. Kim MM, Wu S, Lin SX, et al. Transperineal multiparametric magnetic resonance imaging-ultrasound fusion targeted prostate biopsy combined with standard template improves prostate cancer detection. *J Urol.* 2022;207(1):86-94.
  27. Patel HD, Koehne EL, Shea SM, et al. Systematic versus targeted magnetic resonance imaging/ultrasound fusion prostate biopsy among men with visible lesions. *J Urol.* 2022;207(1):108-117.
  28. Wagensveld IM, Osses DF, Groenendijk PM, et al. A prospective multicenter comparison study of risk-adapted ultrasound-directed and magnetic resonance imaging-directed diagnostic pathways for suspected prostate cancer in biopsy-naïve men. *Eur Urol.* 2022; doi: 10.1016/j.euro.2022.03.003.
  29. Grey ADR, Scott R, Shah B, et al. Multiparametric ultrasound versus multiparametric MRI to diagnose prostate cancer (CADMUS): a prospective, multicentre, paired-cohort, confirmatory study. *Lancet Oncol.* 2022;23(3):428-438.
  30. Immerzeel J, Israel B, Bomers J, et al. Multiparametric magnetic resonance imaging for the detection of clinically significant prostate cancer: what urologists need to know. Part 4: transperineal magnetic resonance-ultrasound fusion guided biopsy using local anesthesia. *Eur Urol.* 2022;81(1):110-117.
  31. Hope TA, Calais J. PSMA PET in prostate cancer—a biomarker or a surrogate endpoint? Reply. *JAMA Oncol.* 2022;8(4):1.
  32. Parry MG, Nossiter J, Morris M, et al. Comparison of the treatment of men with prostate cancer between the US and England: an international population-based study. *Prostate Cancer Prostatic Dis.* 2022; doi: 10.1038/s41391-021-00482-6.
  33. Press BH, Jones T, Olawoyin O, et al. Association between a 22-feature genomic classifier and biopsy Gleason upgrade during active surveillance for prostate cancer. *Eur Urol Open Sci.* 2022;37:113-119.
  34. Jairath NK, Dal Pra A, Vince R, Jr, et al. A systematic review of the evidence for the decipher genomic classifier in prostate cancer. *Eur Urol.* 2021;79(3):374-383.
  35. Beckmann KR, Bangma CH, Helleman J, et al. Comparison of outcomes of different biopsy schedules among men on active surveillance for prostate cancer: an analysis of the G.A.P.3 Global Consortium database. *Prostate.* 2022;82(7):876-879.
  36. de la Calle CM, Shee K, Chu CE, Cowan JE, Nguyen HG, Carroll PR. Association of age with risk of adverse pathological findings in men undergoing delayed radical prostatectomy following active surveillance. *Urology.* 2021;155:91-95.
  37. Press BH, Khajir G, Ghabili K, et al. Utility of PSA density in predicting upgraded Gleason score in men on active surveillance with negative MRI. *Urology.* 2021;155:96-100.
  38. Sayyid RK, Klotz L, Benton JZ, et al. Influence of sociodemographic factors on definitive intervention among low-risk active surveillance patients. *Urology.* 2021;155:117-123.
  39. Timilshina N, Komisarenko M, Martin LJ, et al. Factors associated with discontinuation of active surveillance among men with low-risk prostate cancer: a population-based study. *J Urol.* 2021;206(4):903-913.
  40. Waisman Malaret AJ, Chang P, Zhu K, et al. Evaluating the outcomes of active surveillance in grade group 2 prostate cancer: prospective results from the Canary PASS Cohort. *J Urol.* 2022;207(4):805-813.
  41. Agochukwu-Mmonu N, Qi J, Dunn RL, et al. Patient- and surgeon-level variation in patient-reported sexual function outcomes following radical prostatectomy over 2 years: results from a statewide surgical improvement collaborative. *JAMA Surg.* 2022;157(2):136-144.
  42. Wallis CJD, Zhao Z, Huang LC, et al. Association of treatment modality, functional outcomes, and baseline characteristics with treatment-related regret among men with localized prostate cancer. *JAMA Oncol.* 2022;8(1):50-59.
  43. Perera M, Tin A, Beech B, et al. Oncologic outcomes of men with adverse pathology and biochemical persistence after radical prostatectomy. Presented at annual meeting of the Society of Urologic Oncology. Orlando, Florida, December 1-3, 2021.
  44. Ma TM, Romero T, Nickols NG, et al. Comparison of response to definitive radiotherapy for localized prostate cancer in Black and White men: a meta-analysis. *JAMA Netw Open.* 2021;4(12):e2139769.
  45. Kishan AU, Sun Y, Hartman H, et al. Androgen deprivation therapy use and duration with definitive radiotherapy for localised prostate cancer: an individual patient data meta-analysis. *Lancet Oncol.* 2022;23(2):304-316.
  46. Maitre P, Sood S, Pathare P, et al. Timing of Ga68-PSMA PETCT and patterns of recurrence after prostate radiotherapy: implications for potential salvage. *Radiother Oncol.* 2022;169:71-76.
  47. Crook J, Rodgers J, Pisansky T, et al. Salvage low dose rate prostate brachytherapy: clinical outcomes of a phase II trial for local recurrence after external beam radiotherapy (NRG/RTOG-0526). *Int J Radiat Oncol Biol Phys.* 2020;108(suppl 3):S3.
  48. Turchan WT, Cutright D, Wu T, et al. Hematuria following post-prostatectomy radiotherapy: incidence increases with long-term followup. *J Urol.* 2022;207(6):1236-1245.
  49. Schmidt AL, Tucker MD, Bakouny Z, et al. Association between androgen deprivation therapy and mortality among patients with prostate cancer and COVID-19. *JAMA Netw Open.* 2021;4(11):e2134330.
  50. Attard G, Murphy L, Clarke NW, et al. Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol. *Lancet.* 2022;399(10323):447-460.
  51. Lopes RD, Higano CS, Slovin SF, et al. Cardiovascular safety of degarelix versus leuprolide in patients with prostate cancer: the primary results of the PRONOUNCE randomized trial. *Circulation.* 2021;144(16):1295-1307.
  52. Spetsieris N, Boukvala M, Alafis I, et al. Abiraterone acetate plus prednisone in non-metastatic biochemically recurrent castration-naïve prostate cancer. *Eur J Cancer.* 2021;157:259-267.
  53. Smith MR, Hussain M, Saad F, et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. *N Engl J Med.* 2022;386(12):1132-1142.
  54. Marar M, Long Q, Mamtani R, Narayan V, Vapiwala N, Parikh RB. Outcomes among African American and non-Hispanic White men with metastatic castration-resistant prostate cancer with first-line abiraterone. *JAMA Netw Open.* 2022;5(1):e2142093.
  55. Sweeney C, Bracarda S, Sternberg CN, et al. Ipatasertib plus abiraterone and prednisolone in metastatic castration-resistant prostate cancer (IPATential150): a multicentre, randomised, double-blind, phase 3 trial. *Lancet.* 2021;398(10295):131-142.
  56. Denmeade SR, Wang H, Agarwal N, et al. TRANSFORMER: a randomized phase II study comparing bipolar androgen therapy versus enzalutamide in asymptomatic men with castration-resistant metastatic prostate cancer. *J Clin Oncol.* 2021;39(12):1371-1382.
  57. Powles T, Yuen KC, Gillessen S, et al. Atezolizumab with enzalutamide versus enzalutamide alone in metastatic castration-resistant prostate cancer: a randomized phase 3 trial. *Nat Med.* 2022;28(1):144-153.
  58. Vogelzang NJ, Beer TM, Gerritsen W, et al. Efficacy and safety of autologous dendritic cell-based immunotherapy, docetaxel, and prednisone vs placebo in patients with metastatic castration-resistant prostate cancer: the VIABLE phase 3 randomized clinical trial. *JAMA Oncol.* 2022;8(4):546-552.
  59. Schweizer MT, Sivakumar S, Tukachinsky H, et al. Concordance of DNA repair gene mutations in paired primary prostate cancer samples and metastatic tissue or cell-free DNA. *JAMA Oncol.* 2021;7(9):1378-1382.

## AUA2022 COURSE

# Localized Prostate Cancer: AUA/ASTRO Guideline 2022

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## Learning Objective

*At the conclusion of the activity, participants will be able to highlight recent guideline updates in management of clinically localized prostate cancer.*

Prostate cancer remains the most common noncutaneous cancer among U.S. men, with an estimated 268,490 new cases and 34,500 deaths in 2022.<sup>1</sup> The majority of newly diagnosed patients have clinically localized disease.<sup>1</sup> Providing evidence-based guideline statements to support clinical decision making represents an important component of delivering high-quality care. Given the recent breadth of investigation into various aspects of the evaluation and management of clinically localized prostate cancer (CLPC), the AUA, in collaboration with ASTRO (American Society for Radiation Oncology), updated the organization's prior guideline. The 2022 iteration was presented at the 2022 AUA Annual Meeting as an Instructional Course, which summarized current evidence and provided specific guidance for physicians in the management of CLPC.

A critical component of the Guidelines is the recognition that the selection of a management strategy for CLPC is preference-sensitive and includes patients' interpretation of treatment-specific risks and benefits. The Guidelines thereby emphasize a collaborative, shared decision-making (SDM) process.

In addition, the Guidelines includes specific guidance on risk assessment and staging, risk-based management, principles of active surveillance (AS), surgery, and radiation, and recommendations for followup after treatment.<sup>2</sup>

## Risk Assessment and Staging

An important component of the updated Guideline is the continued utilization of a risk group classification for patients with newly diagnosed CLPC. The intention of risk stratification is to facilitate patient counseling regarding the severity of disease and documented natural history. Such perspective facilitates SDM, to allow consideration of the tradeoffs between treatment-related side effects and the likelihood of disease progression. Furthermore, determining disease risk informs the intensity of the staging evaluation, management options, and allows assessment of clinical trial eligibility.

While recognizing that risk groups may be updated as new information is gained, the current Guideline risk group criteria include the clinical T stage (determined by digital rectal examination [DRE]), serum PSA, Grade Group (Gleason score), and tumor volume on biopsy (see Table).

Imaging studies are intended to define the local extent of disease as well as determine the presence of nodal and distant metastases, and thereby inform management. As such, clinicians should use a risk-based approach to staging for patients with newly diagnosed prostate cancer.

## Risk-Based Management

Outlining the likelihood of both cancer control and the recognized risks or side effects associated with each management strategy for CLPC facilitates SDM. Indeed, tools are available to estimate the likelihood of functional

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**Table.** Risk group classification

Low-Risk	PSA <10 ng/ml AND Grade Group 1 AND clinical stage T1-T2a
Intermediate-risk	PSA 10–<20 ng/ml OR Grade Group 2-3 OR clinical stage T2b-c <ul style="list-style-type: none"> <li>• Favorable: Grade Group 1 with PSA 10–&lt;20 ng/ml or clinical stage T2b-c and &lt;50%* biopsy cores positive OR Grade Group 2 with PSA &lt;10 ng/ml and clinical stage T1-2a and &lt;50% biopsy cores positive</li> <li>• Unfavorable: Grade Group 1 with PSA 10–&lt;20 ng/ml and clinical stage T2b-c OR Grade Group 2 with PSA 10–&lt;20 ng/ml and/or clinical stage T2b-c and/or ≥50%* biopsy cores positive OR Grade Group 3 with PSA &lt;20 ng/ml</li> </ul>
High-risk	PSA ≥20 ng/ml OR Grade Group 4-5 OR clinical stage T3

\*Percent biopsy cores positive is the total number of cores containing cancer divided by total number of cores obtained × 100. This is not the percentage of cancer within a positive core. Regarding assessment of the percent biopsy cores positive for risk stratification, the Panel acknowledges that with the increasing use of pre-biopsy MRI and subsequent targeted biopsies, multiple cores may be obtained from a targeted lesion. Multiple cores from the same lesion should be considered as a single core (ie for the calculation of percentage cores positive in risk assessment). If all cores are negative, that is considered a single negative core. If 1 or more cores from the same lesion are positive, that is considered a single positive core, with the highest Gleason score used for risk stratification.

outcomes with each treatment.<sup>3</sup> The Guidelines provide risk-based recommendations for management, with strategies mentioned including AS, surgery, radiation, ablation, and systemic therapy. The Guideline further discusses appropriate patient selection for watchful waiting, a strategy that does not involve routine cancer surveillance, but rather aims to deliver palliative therapy for relief of symptoms should they develop. Watchful waiting is appropriate for asymptomatic elderly patients or patients with significant comorbidities in whom competing risks of mortality are considerably greater than the risk of death from prostate cancer.

## Principles of AS

While AS is the preferred management option for most low-risk patients, those electing this option need to be counseled regarding the importance of continued followup as part of this approach. Specifically, patients on AS should undergo PSA testing (no more frequently than every 6 months), updated symptom assessment, and physical examination with DRE every 1 to 2 years. Serial PSA increases, new DRE abnormalities, or other concerns for clinical progression should prompt reevaluation with MRI and possible prostate biopsy; less frequently, direct conversion to treatment may be considered. Importantly, the Panel believes that while multiparametric MRI may be used to augment risk stratification for patients managed with AS, MRI should not replace periodic surveillance biopsies.

## Principles of Surgery

While several recommendations regarding surgery remain unchanged from previous Guideline iterations, the 2022 Guideline was informed by inclusion of greater followup data as well as further discussion of pelvic lymphadenectomy. For example, the Guideline advises the use of nomograms to select patients for pelvic lymphadenectomy.<sup>4</sup> In addition, when the decision is made to perform pelvic lymphadenectomy, the Panel recommends an extended lymph node dissection because of its incremental staging benefit versus a limited dissection.<sup>5</sup> At the same time, the updated

Guideline also acknowledges that while pelvic lymphadenectomy is useful for staging and may provide valuable information to guide future management with secondary therapies, an oncologic benefit to lymphadenectomy has not been well established.<sup>6,7</sup> Indeed, to date, randomized studies have not compared the relative oncologic outcomes among patients undergoing extended lymph node dissection (performed according to a standardized template) at the time of prostatectomy versus patients undergoing no lymph node dissection at the time of prostatectomy specifically in a high-risk cohort.

## Principles of Radiation

As with surgery, many statements regarding radiation remain unchanged from the previous Guideline iteration; however, the new Guideline does provide detailed discussion of options for men with higher-risk disease, which may include newer forms of radiation therapy and details regarding the indications for combination with androgen deprivation therapy (ADT).

In looking at the role of lymph node irradiation among patients electing radiation therapy, the Guideline notes the lack of benefit in low- and intermediate-risk patients from prospective trials. At the same time, based on recent trial data, the Guideline does state that nodal radiation may be offered to high-risk patients.<sup>8,9</sup> Indeed, inclusion of pelvic lymph nodes in the radiation field has been associated with improvements in biochemical recurrence and distant metastases. The Panel recognizes that while previous trials did not demonstrate a benefit to nodal radiation, many of those studies were limited by variably defined high-risk subgroups, use of simpler radiation technologies with more limited pelvic fields, shorter durations of ADT, and delivery of lower radiation doses to the prostate.

Importantly, the Guideline highlights the judicious use of ADT with radiation by outlining risk-based indications for and duration of ADT among patients electing radiation therapy. Indeed, the well-recognized adverse effects of ADT, which in turn may potentially negatively impact patients' quality of life, must be considered. As such, the Panel believes that patients

being offered ADT should be aware of these side effects.

## Follow-up after Treatment

Monitoring after treatment is necessary to identify recurrence as well as complications from treatment, and thereby facilitate early intervention as appropriate. The Panel therefore included recommendations regarding initial and ongoing monitoring and highlighted the importance of routine discussion of urinary, bowel, and sexual function with the use of standardized/validated instruments.

Further, it was acknowledged that clinicians should also support patients with CLPC through continued symptom management and encourage engagement with professional or community-based resources. The array of survivorship needs for an individual patient and caregiver may be broad and should be explored by the clinician and team to ensure that appropriate support, especially peer support, is offered. ■

1. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2022. *CA Cancer J Clin.* 2022;72(1):7-33.
2. Légaré F, Stacey D, Turcotte S, et al. Interventions for improving the adoption of shared decision making by healthcare professionals. *Cochrane Database Syst Rev.* 2014;(9):CD006732.
3. Laviana AA, Zhao Z, Huang L, et al. Development and internal validation of a web-based tool to predict sexual, urinary, and bowel function longitudinally after radiation therapy, surgery, or observation. *Eur Urol.* 2020;78(2):248-255.
4. Gandaglia G, Soligo M, Battaglia A, et al. Which patients with clinically node-positive prostate cancer should be considered for radical prostatectomy as part of multimodal treatment? The impact of nodal burden on long-term outcomes. *Eur Urol.* 2019;75(5):817-825.
5. Clark T, Parekh DJ, Cookson MS, et al. Randomized prospective evaluation of extended versus limited lymph node dissection in patients with clinically localized prostate cancer. *J Urol.* 2003;169(1):145-147.
6. Chen J, Wang Z, Zhao J, et al. Pelvic lymph node dissection and its extent on survival benefit in prostate cancer patients with a risk of lymph node invasion >5%: a propensity score matching analysis from SEER database. *Sci Rep.* 2019;9:17985.
7. Fossati N, Willemsse P-PM, Van den Broeck T, et al. The benefits and harms of different extents of lymph node dissection during radical prostatectomy for prostate cancer: a systematic review. *Eur Urol.* 2017;72(1):84-109.
8. Pommier P, Chabaud S, Lagrange JL, et al. Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Update of the long-term survival results of the GETUG-01 randomized study. *Int J Radiat Oncol.* 2016;96(4):759-769.
9. Murthy V, Maitre P, Kannan S, et al. Prostate-only versus whole-pelvic radiation therapy in high-risk and very high-risk prostate cancer (POP-RT): outcomes from phase III randomized controlled trial. *J Clin Oncol.* 2021;39(11):1234-1242.

## AUA2022 COURSE

## AUA Guidelines on Advanced Prostate Cancer

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## Learning Objective

*At the conclusion of the activity, participants will be able to describe the various disease states comprising advanced prostate cancer and advancement in management.*

Advanced prostate cancer (APC) is a diverse disease state encompassing biochemical recurrence, metastatic hormone sensitive prostate cancer (mHSPC), nonmetastatic castration-resistant prostate cancer (nmCRPC), and metastatic castration-resistant prostate cancer (mCRPC). Over the past several decades many advances have yielded improvements in patient quality of life and survival, but still prostate cancer accounts for 11% of all cancer-related death in men in the United States.<sup>1</sup> This AUA2022 course highlighted the current and rapidly evolving diagnostic and treatment landscape for men with APC.

It is well established that prostate cancer is an androgen-driven disease, and in patients with APC, androgen deprivation therapy (ADT) remains the mainstay of treatment. However, the course reviewed updated Guidelines which note that men with biochemical recurrence alone should not routinely initiate ADT. When considering factors such as total PSA, PSA doubling time, and patient comfort, ADT may be initiated in select, truly high-risk patients. In the absence of metastatic disease, intermittent ADT may be considered, given noninferior overall survival (OS) and improved patient quality of life, and in fact this is the one place the Guidelines consider intermittent ADT.<sup>2</sup>

The course reviewed exciting and rapidly advancing management options for patients with mHSPC. Discussion centered on important treatment-related considerations like baseline PSA, PSA velocity, patient symptomatology, prior therapy, disease volume, and genetic test results. Regarding disease extent, the CHAARTED definition of high-volume (visceral metastasis and/or 4+ bone metastases with at least 1 beyond pelvis and vertebral column) and low-volume disease were reviewed, noting the impact of disease burden on response to therapy.<sup>3</sup> Additionally, for mHSPC and throughout the continuum of APC, we discussed the recommendation for germline testing and genetic counseling. This is particularly important given that newly diagnosed metastatic patients have an ~12% chance of harboring an inherited DNA repair gene mutation—a scenario where cascade counseling may be beneficial.<sup>4</sup>

The course stressed that, while androgen deprivation with medical or surgical castration is essential, no longer is “ADT alone” the standard of care in men with mHSPC. We reviewed robust, high-level evidence demonstrating that either docetaxel chemotherapy or an androgen pathway directed therapy like abiraterone, apalutamide, or enzalutamide in combination with ADT improves survival. CHAARTED stratified men according to several factors including extent of metastatic disease and performance status prior to randomization. Results indicated improved OS with the addition of docetaxel and a more robust advantage in high-volume patients.<sup>3</sup> Similarly, in STAMPEDE, patients who received docetaxel with ADT experienced a highly significant OS benefit although there was no survival difference by volume status, likely reflecting differences in the study populations.<sup>5</sup> Abiraterone, a potent androgen synthesis inhibitor, is also approved for treatment of mHSPC based on LATITUDE, which demonstrated OS and progression-free survival ben-

“The course stressed that, while androgen deprivation with medical or surgical castration is essential, no longer is “ADT alone” the standard of care in men with mHSPC.”

efits, and STAMPEDE, with an OS benefit favoring combination therapy over ADT alone.<sup>6,7</sup> And finally, we reviewed the androgen receptor-targeted treatments that have established superiority over ADT alone with apalutamide in the TITAN trial, and enzalutamide in ARCHES and ENZAMET.<sup>8-10</sup> We noted that local therapy may benefit select patients with low-volume mHSPC based on STAMPEDE, but additional data are needed prior to offering surgery to men with metastatic disease.<sup>11</sup>

The course also highlighted new data not yet included in the Guidelines but likely to be reflected in upcoming revisions regarding “treatment intensification” in mHSPC. A recent multicentered 4-arm, phase III trial, PEACE-1, evaluated the potential benefit of adding abiraterone to ADT and docetaxel, with or without radiation.<sup>12</sup> Results were highly significant with improvements in radiographic progression-free survival and OS. Subgroup analysis showed a benefit in both high- and low-volume patients, although intensification yielded more adverse events including hypertension and liver toxicity. ARASENS also examined treatment intensification with the addition of darolutamide to ADT and docetaxel.<sup>13</sup> This international, randomized, double-blind, placebo-controlled trial again demonstrated a highly sig-

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nificant survival benefit without any increase in adverse events. The benefit of treatment intensification for mHSPC is intriguing, but there remain unanswered questions regarding the potential for overtreatment and increased side effects. Ultimately, an adaptive treatment approach may be required with consideration of fitness for chemotherapy, symptom burden, cost, patient preference, disease volume, and histological or molecular features. One consideration may be its use for this triple therapy in select patients who present with de novo high-volume metastatic disease for example.

We then reviewed management of patients with nmCRPC, focusing on 3 trials evaluating androgen-targeted therapies in men with a rapid PSA doubling time ( $\leq 10$  months) at high risk for metastasis. In SPARTAN, apalutamide was compared to placebo, and initial publication demonstrated a significant delay in metastasis-free survival (MFS) while mature data indicated a survival benefit.<sup>14,15</sup> With a similar trial design and outcome, PROSPER results showed improved MFS with enzalutamide and ultimately a risk of death 27% lower than with placebo.<sup>16,17</sup> Darolutamide with ADT was compared to placebo for M0 castration-resistant prostate cancer patients in ARAMIS, again yielding impressive MFS and OS benefits.<sup>18</sup>

Over the past several years, numerous therapies have emerged offering a survival benefit for men with mCRPC, a disease generally associated with poor outcomes. Many of these agents were first approved in this advanced state and have since “moved up” earlier in the disease continuum as discussed above,

“The benefit of treatment intensification for mHSPC is intriguing, but there remain unanswered questions regarding the potential for overtreatment and increased side effects.”

including docetaxel, abiraterone, and enzalutamide.<sup>19,21</sup> We reviewed the mechanism of action and data in support of the novel immunotherapeutic sipuleucel-T and the radiopharmaceutical radium-223, both of which have demonstrated an OS advantage for specific mCRPC patient subsets.<sup>22,23</sup>

One of the most exciting recent advancements in mCRPC highlighted at this year’s course was the approval of poly(adenosine diphosphate-ribose) polymerase inhibitors. These novel drugs target defects in DNA repair genes in mCRPC patients, resulting in antitumor activity and more favorable outcomes. In the phase III PROfound trial, patients with prespecified gene alterations experienced improved clinical outcomes (radiographic progression-free survival, OS) with olaparib following progression through at least 1 novel androgen directed therapy.<sup>24</sup> In the TRITON2 study, rucaparib benefited patients with germline or somatic BRCA1/2 alterations who had progressed through both a second-generation antiandrogen- and taxane-based chemotherapy.<sup>25</sup> Here again we reviewed the importance of somatic and genetic testing in conjunction with genetic counseling.

Throughout the course, faculty discussed the development and implications of and indications for next-generation imaging in APC. Specifically, prostate-specific membrane antigen (PSMA) positron emission tomography (PET) was noted to be an absolute gamechanger, altering the way we evaluate patients and, soon, how we treat the disease (theranostics). In December 2020, the U.S. Food and Drug Administration approved the first PSMA-targeted PET imaging drug (Ga 68 PSMA-11) for men with prostate cancer and a rising PSA after failed local therapy. This approval was based on data indicating that PSMA PET offers a high positive predictive value and provides important information that impacts therapeutic approach, even at very low PSA values.<sup>26</sup> In May 2021, the U.S. Food and Drug Administration approved a second PSMA-targeted PET imaging drug for men with prostate cancer (piflufolostat F18) based on 2 studies. In the CONDOR study, men with a rising PSA after failed local therapy underwent <sup>18</sup>F-DCFPyL-PET, which resulted in a change in manage-

ment.<sup>27</sup> In OSPREY, 2 populations were examined—those with high-risk prostate cancer undergoing prostatectomy with lymphadenectomy and those with rising PSA after prior local therapy.<sup>28</sup> Again, results indicated a high positive predictive value. Likely, many patients with APC previously considered nonmetastatic will now be reclassified as metastatic. We must also consider that the use of PSMA PET may not change the way patients respond to therapy. We expect updated guidelines and future courses to address advanced imaging in further detail.

So, the landscape for men with APC continues to evolve. Key themes that will be further explored as we go forward include moving effective agents up earlier in the disease state, treatment intensification and combinations that have different mechanisms of action, and a greater role for precision medicine. We are also beginning to get a much clearer picture on treatment sequencing, particularly in the mCRPC disease state. We look forward to crafting many of these updates and new trial information into a revised AUA Guidelines for APC this year, so stay tuned. ■

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022;72(1):7-33.
2. Crook JM, O’Callaghan CJ, Duncan G, et al. Intermittent androgen suppression for rising PSA level after radiotherapy. *N Engl J Med*. 2012;367(10):895-903.
3. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med*. 2015;373(8):737-746.
4. Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *N Engl J Med*. 2016;375(5):443-453.
5. James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage platform randomized controlled trial. *Lancet*. 2016;387(10024):1163-1177.
6. Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2017;377(4):352-360.
7. James ND, de Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. *N Engl J Med*. 2017;377(4):338-351.
8. Chi KN, Agarwal N, Bjartall A, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2019;381(1):13-24.
9. Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. *J Clin Oncol*. 2019;37(32):2974-2986.

10. Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. *N Engl J Med.* 2019;381(2):121-131.
11. Parker CC, James NJ, Brawley CD, et al. Radiotherapy to the primary tumour for newly diagnosed metastatic prostate cancer (STAMPEDE): a randomized controlled phase 3 trial. *Lancet.* 2018;392(10162):2353-2366.
12. Fizazi K, Carles-Galceran J, Foulon S, et al. A phase III trial with a 2x2 factorial design in men with de novo metastatic castration sensitive prostate cancer: overall survival with abiraterone acetate plus prednisone in PEACE-1. *Ann Oncol.* 2021;39(15 suppl):5000.
13. Smith MR, Hussain M, Saad F, et al. Darolutamide and survival in metastatic, hormone sensitive prostate cancer. *N Engl J Med.* 2022;386(12):1132-1142.
14. Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis free survival in prostate cancer. *N Engl J Med.* 2018;378(15):1408-1418 (SPARTAN).
15. Smith MR, Saad F, Chowdhury S, et al. Apalutamide and overall survival in prostate cancer. *Eur Urol.* 2021;79(1):150-158 (SPARTAN).
16. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *N Engl J Med.* 2018;378(26):2465-2472.
17. Sternberg CN, Fizazi K, Saad F, et al. Enzalutamide and survival in nonmetastatic castration-resistant prostate cancer. *N Engl J Med.* 2020;382(23):2197-2206.
18. Fizazi K, Shore N, Tammela TL, et al. Non-metastatic, castration-resistant prostate cancer and survival with darolutamide. *N Engl J Med.* 2020;383(11):1040-1049.
19. Tannock IF, De Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med.* 2004;351(15):1502-1512.
20. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without prior chemotherapy. *N Engl J Med.* 2013;368(2):138-148.
21. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med.* 2014;371(5):424-433.
22. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med.* 2010;363(5):411-422.
23. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med.* 2013;369(3):213-223.
24. de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med.* 2020;382(22):2091-2102.
25. Abida W, Patnaik A, Campbell D, et al. Rucaparib in men with metastatic castration-resistant prostate cancer harboring a BRCA1 or BRCA2 gene alteration. *J Clin Oncol.* 2020;38(32):3763-3772.
26. Fendler WP, Calais J, Eiber M, et al. Assessment of <sup>68</sup>Ga-PSMA-11 PET accuracy in localizing recurrent prostate cancer: a prospective single-arm clinical trial. *JAMA Oncol.* 2019;5(6):856-863.
27. Morris MJ, Rowe SP, Gorin MA, et al. Diagnostic performance of <sup>18</sup>F-DCFPyL-PET/CT in men with biochemically recurrent prostate cancer: results from the CONDOR phase III, multicenter study. *Clin Cancer Res.* 2021;27(13):3674-3682.
28. Pienta KJ, Gorin MA, Rowe SP, et al. A phase 2/3 prospective multicenter study of the diagnostic accuracy of prostate specific membrane antigen PET/CT with <sup>18</sup>F-DCFPyL in prostate cancer patients (OSPREDY). *J Urol.* 2021;206(1):52-61.

## AUA2022 COURSE

# The Changing Face of Advanced Prostate Cancer 2022

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## Learning Objective

*At the conclusion of the activity, participants will be able to discuss new treatment available for patients with newly diagnosed M1 prostate and new treatment available for patients with M0 metastatic castrate-resistant prostate cancer.*

As the course director, I have been fortunate to host a course on advanced prostate cancer at the AUA Annual Meeting since 2012, and the changes over these 10+ years have been nothing less than spectacular!<sup>1</sup> Furthermore, the last several years have been “interesting,” with this being the first “live” AUA since 2019 due to COVID. It was exciting being back in front of a live audience. Furthermore, Dr. Karsh and I welcomed genitourinary medical oncologist superstar Dr. Alicia Morgans to the course, and she deliv-

ered a wonderful talk and great panel discussion.

In the years from 2012 to 2015, it was all about metastatic castrate-resistant prostate cancer (CRPC) with multiple new therapeutic advances starting in 2010 (sipuleucel-T) followed by abiraterone and enzalutamide and a focus on bone-targeted agents. Later, we expanded to cover hormone-sensitive (HS) advanced disease due to the new data on docetaxel and abiraterone extending survival in new M1 patients. In 2017, we added the topic of nonmetastatic CRPC (M0 CRPC) due to emerging data on use of apalutamide and enzalutamide in these men, and data now suggest similar benefit for adding darolutamide as well. Then in 2019, we doubled down on HS new M1 disease with emerging data that 4 agents (docetaxel, abiraterone, apalutamide, and enzalutamide) all improve survival for men with new metastatic prostate cancer.

Now, from 2020 to 2022, we have been going boldly into personalized molecular medicine with the addition of both hereditary and somatic testing for cancer-associated gene alterations and several therapeutic agents U.S.

Food and Drug Administration (FDA)-approved in the past several years based on this molecular testing.

## Newly Diagnosed HS M1 Prostate Cancer

Seven years ago hormone-naïve/HS newly diagnosed metastatic (M1) prostate cancer became hot news with the release of the CHAARTED trial data in 2015 and the STAMPEDE trial results in 2016 showing a benefit of up-front docetaxel chemotherapy in new M1 disease.<sup>2,3</sup> Primary androgen deprivation therapy (ADT) had been the only treatment for men with new M1 disease for more than three-quarters of a century. In the last few years CHAARTED and STAMPEDE taught us that adding 6 cycles of docetaxel within 4 months of starting hormone therapy/ADT resulted in a major survival benefit. For high-volume disease (4 or more bone metastases and/or visceral metastases) the addition of chemotherapy resulted in a 17-month survival advantage compared to ADT

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alone. However, the initial publication hazard ratio generally supported a benefit of docetaxel for low-volume M1 disease as well. The STAMPEDE trial confirmed the benefit of docetaxel and generally supported the use of chemotherapy for all men with new M1 disease. Median overall survival (OS) was 65 months for men randomized to receive docetaxel vs 43 months for men randomized to standard of care ADT alone. In 2018, Kyriakopoulos et al reported longer-term followup from CHAARTED confirming the benefit of docetaxel for high-volume disease but not supporting up-front chemotherapy for low-volume disease.<sup>4</sup>

In 2017 the LATITUDE trial showed that abiraterone added to ADT for men with new M1 disease resulted in a similar survival benefit to docetaxel.<sup>5</sup> In 2019, we learned that both apalutamide and enzalutamide also significantly extend survival compared to traditional ADT alone.<sup>6-8</sup> The results of TITAN (apalutamide) and ENZAMET and ARCHES (NCT02677896; enzalutamide) were published showing robust benefits. In my mind, this is “combined androgen blockade” (CAB) or “maximal androgen blockade” (MAB) finally showing a survival benefit now using second- and third-generation nonsteroidal antiandrogens (AAs).<sup>9</sup>

In TITAN, 1,052 men were randomized to traditional ADT alone vs ADT plus apalutamide (240 mg orally daily).<sup>6</sup> Ten percent received prior docetaxel, 80% had M1 disease at initial diagnosis, and 63% had high-volume disease. In the final analysis, at a median followup of 44 months, 51% remained on apalutamide.<sup>10</sup> Apalutamide conferred a 35% reduction in risk of death. This benefit was present regardless of disease volume or receipt of docetaxel. At 4 years, OS was 65% in the apalutamide arm and 51.8% in the ADT plus placebo group.

In a similar fashion, ARCHES (NCT02677896) and ENZAMET documented a similar benefit to enzalutamide in new M1 HS disease.<sup>7,8</sup> ARCHES was the FDA-registration trial and enrolled 1,150 new M1 patients receiving testosterone suppression with or without docetaxel, stratified by high- or low-volume disease, with men randomized to enzalutamide (574) vs placebo (576). At ESMO 2021, Armstrong

et al presented the latest trial update. As of the data cutoff of May 28, 2021, 397 (34.5%) patients remained on treatment, with a median followup of 44.6 months. The median treatment duration was 40.2 months on enzalutamide + ADT, 13.8 months on placebo + ADT, and 23.9 months for crossover patients. Enzalutamide + ADT extended survival vs placebo + ADT (HR 0.66; 95% CI 0.53–0.81;  $p < 0.0001$ ).

Apalutamide, darolutamide, and enzalutamide are second-generation nonsteroidal oral AAs and are more potent than first-generation agents (flutamide, nilutamide, and bicalutamide). In past times, adding first generation AA to ADT was called CAB or MAB. The latest studies of second-generation agents finally prove the concept of CAB/MAB, first proposed by Labrie and others in the mid-1980s.<sup>10</sup>

The latest concept discussed by Dr. Karsh at the 2022 course was “triplet” therapy for M1 disease. The PEACE-1 trial reported by Fizazi et al at ESMO 2021 studied ADT plus docetaxel plus abiraterone acetate/prednisone vs ADT plus docetaxel, finding a survival benefit of the triple therapy.<sup>11</sup> The OS benefit was seen across subgroups, including those with high-volume disease (HR 0.72, 95% CI 0.55–0.95) and low-volume disease (HR 0.83, 95% CI 0.50–1.38; data immature). Adding abiraterone acetate/prednisone to ADT plus docetaxel improves both radiographic progression-free survival and OS in metastatic castrate-sensitive prostate cancer men, even when 84% of metastatic CRPC men from the control arm received an androgen-signaling inhibitor. Toxicity was as expected—no new safety concerns were seen in this new triple combination treatment. From a clinical perspective, the benefit was a median lifetime gain of more than 1.5 years for metastatic castrate-sensitive prostate cancer men with high-volume disease (5.1 vs 3.5 years).<sup>11</sup> Finally, ARASENS is a phase III clinical trial of ADT plus docetaxel plus darolutamide vs ADT plus docetaxel plus placebo that was reported at ASCO GU in February 2022 by Dr. Matthew Smith.<sup>12</sup> There was an OS in favor of the triple therapy including darolutamide for both *de novo* M1 and recurrent M1 disease reported.

## CRPC

Since 2010, multiple new agents have been approved by the FDA for M1 CRPC, including sipuleucel-T, cabazitaxel, abiraterone acetate, denosumab, enzalutamide, and radium-223. Except for cabazitaxel, all of these agents are commonly available for urologists and oncologists to prescribe. The latest advances are olaparib, rucaparib, and pembrolizumab for patients with somatic or germline mutations in actionable genes implicated in advanced prostate cancer.<sup>13-16</sup>

## Bone Health/Denosumab

Denosumab (trade name Xgeva<sup>®</sup>) is prescribed at a dose of 120 mg subcutaneously monthly to prevent skeletal-related events in men with M1 CRPC with bone metastases.<sup>17</sup> The FDA also approved a 60 mg dose (trade name Prolia<sup>®</sup>) subcutaneously twice a year to prevent bone loss (osteopenia and osteoporosis) in men without bone metastases who are on gonadotropin-releasing hormone analogue therapy for prostate cancer. We continue to remind urologists to be mindful of using supportive agents including vitamin D and calcium supplements, and monitoring for osteopenia and osteoporosis with annual dual energy x-ray absorptiometry scanning.

## Sipuleucel-T

Sipuleucel-T is a novel immunotherapy approved by the FDA in 2010 for

“Since 2010, multiple new agents have been approved by the FDA for M1 CRPC, including sipuleucel-T, cabazitaxel, abiraterone acetate, denosumab, enzalutamide, and radium-223.”

asymptomatic or minimally symptomatic M1 CRPC.<sup>18</sup> The ideal patient for sipuleucel-T should have documented clinical metastases and a rising PSA while on continuous hormonal therapy. The patient should not have bone or cancer pain requiring narcotic pain medications. In men with PSA levels in the lowest quartile of the IMPACT trial (PSA less than 22 ng/ml) there was a more robust OS advantage to sipuleucel-T. Specifically, the estimated 3-year survival in this group of treated patients was 62.6% compared to 41.6% for men randomized to the control arm of the study.<sup>19</sup> The PROSEED registry of 1,902 patients treated with sipuleucel-T in real-world practice between 2011 and 2014 has also provided confirmatory data. In a respective analysis of 219 African American men disease-matched to a Caucasian cohort, OS was 35.3 months vs 25.8 months.<sup>20</sup> These intriguing data need to be confirmed in prospective fashion.

## Abiraterone

Abiraterone is a 17-lyase and 17-hydroxylase inhibitor that blocks key pathways in the steroidal synthesis pathways leading to androgen production.<sup>21</sup> Low-dose prednisone (5 to 10 mg daily is a physiological dose) is recommended to be administered with abiraterone to help limit overproduction of aldosterone and limit the side effects of hypertension, hypokalemia, and fluid retention. The FDA-approved indication for abiraterone is before or after docetaxel chemotherapy in men with M1 CRPC based on evidence from the Cougar-AA-301 and -302 clinical trials. The dose for abiraterone is 1,000 mg orally once daily in the fasted state along with low-dose steroid (5 mg prednisone orally twice daily). The final analyses of both trials were reviewed, showing clinically meaningful end points of OS and radiographic progression-free survival (Cougar-302) benefits. Abiraterone is also available in a 500 mg oral dose, which allows for 2 rather than 4 pills per day, which might help with compliance for some men.

Abiraterone was also FDA approved for use in men with newly diagnosed HS M1 prostate cancer in February 2018.<sup>22</sup> Approval was based on LATITUDE (NCT01715285), a placebo-con-

trolled international clinical trial that randomized 1,199 patients with metastatic high-risk HS disease. Patients received 1,000 mg abiraterone acetate orally once daily with 5 mg prednisone once daily (in 597) or matching placebo orally once daily (in 602). Patients in both arms received a gonadotropin-releasing hormone analogue or underwent bilateral orchiectomy. The major efficacy end point was OS. Median OS was inestimable and 34.7 months in the abiraterone acetate and placebo arms, respectively (HR 0.621; 95% CI 0.509, 0.756;  $p < 0.0001$ ). Median duration of abiraterone use was 24 months.

## Enzalutamide

Enzalutamide, a second-generation androgen receptor antagonist, was FDA approved in 2012 to treat men with disease who progressed after docetaxel based chemotherapy based on level 1 evidence from the AFFIRM trial.<sup>23</sup> It received expanded approval in 2014 for use before chemotherapy in the PREVAIL trial. Enzalutamide is taken orally at a dose of 160 mg daily with or without food and it does not require prednisone. However, enzalutamide does have an approximately 0.5%–1% risk of seizures associated with its use and crosses the blood-brain barrier, implicating it with some risk of falls and fatigue.

PROSPER is a phase III, randomized, double-blind, placebo-controlled study of enzalutamide in men with M0 CRPC.<sup>24</sup> It demonstrated an approximately 2-year metastasis-free survival (MFS) benefit over placebo, showing that MFS is a meaningful end point. As of July 13, 2018, enzalutamide was the second FDA-approved drug for M0 CRPC. Updated data from PROSPER in 2020 confirmed an OS benefit.<sup>25</sup>

In the setting of M1 HS disease, enzalutamide is also FDA approved based on ARCHES and ENZAMET, as noted earlier.

## Apalutamide

As previously noted, apalutamide, with a mechanism of action similar to enzalutamide, was the first drug for M0 CRPC approved by the FDA, which occurred in February 2018.<sup>26</sup> The data from the SPARTAN trial showed that

apalutamide delayed MFS by about 2 years. Overall the drug was very well tolerated. Unique side effects included maculopapular rash in 24% of patients, but only 5% were grade 3–4. The rash usually resolved with topical lotions, drug holiday, and temporary dose reduction. Approximately 4% of patients required systemic corticosteroids. In addition, 8% of patients had decreases in thyroid hormone (considered chemical hypothyroidism), and there were no grade 3–4 adverse events. The FDA did not mandate thyroid testing in the approval label. Seizure was reported in 2 patients (0.2%).

Apalutamide, as noted earlier, was also proven to extend survival in newly diagnosed HS M1 prostate cancer, and final analysis of the TITAN trial showed a robust 35% improvement in OS compared to ADT alone. The TITAN trial is credited with finally proving the OS benefit of CAB, ending a quest of 30+ years to prove this concept.

Another topic of interest related to use of abiraterone and enzalutamide/apalutamide is molecular profiling. The discovery of the AR-V7 splice variant of the androgen receptor offers an intriguing glimpse of the future of personalized medicine.<sup>27</sup> Specifically, the response to abiraterone or enzalutamide was less robust in men who harbored this variant in circulating tumor cells. In February 2018 Genomic Health, Inc. (Redwood City, California) received FDA approval for the Oncotype DX® AR-V7 Nucleus Detect™ test, a commercially available assay for AR-V7.

## Radium-223

Radium-223 is a parenteral radiopharmaceutical that can be ordered by urologists. It is usually given in a nuclear medicine or radiation oncology department setting, but many large group practices have incorporated it into their centers. It is an alpha-emitting liquid radiation product that received FDA approval in May 2013 based on results from the ALSYMPCA trial.<sup>28</sup> Radium-223 is indicated for the treatment of patients with symptomatic M1 CRPC with bone metastases and no known visceral metastatic disease. The dose regimen is 50 kBq (1.35 microcurie) per

kg body weight, given at 4-week intervals in 6 injections.

Urologists may be familiar with earlier generation beta radiopharmaceuticals such as samarium and strontium. However, radium-223 is different. It is a large molecule alpha particle and does not penetrate the bone marrow to the degree of older agents. In other words, radium-223 is much less likely to cause serious bone marrow toxicity. In addition, the use of radium-223 was associated with an OS benefit whereas the older beta-emitting radiopharmaceuticals were never proven to extend survival. For radium-223 to be associated with improved survival at least 4 monthly cycles must be administered.

Radium-223 should not be used in patients currently being treated with abiraterone/prednisone. The phase III ERA223 trial compared abiraterone/prednisone plus radium-223 vs abiraterone/prednisone plus placebo in patients with asymptomatic or mildly symptomatic chemotherapy-naïve metastatic CRPC. The study was unblinded in late 2017. Bayer, the manufacturer of radium-223, reported that the unblinding followed the recommendation of an independent data monitoring committee that observed an imbalance, with more fractures and deaths in patients receiving radium-223 and abiraterone/prednisone vs abiraterone alone.<sup>29</sup>

## Darolutamide

In mid-2019, darolutamide was FDA approved for M0 CRPC based on the ARAMIS trial, making this the third agent approved (apalutamide, enzalutamide, and darolutamide) in this disease state.<sup>30</sup> This third-generation non-steroidal oral AA prolonged MFS also by approximately 2 years compared to placebo in M0 CRPC and more recently showed an OS advantage.<sup>31</sup> The drug has twice daily oral dosing, which may be a slight disadvantage compared to enzalutamide and apalutamide, but does not appear to cross the blood-brain barrier to the extent of the other 2 agents and is reportedly less apt to cause falls and seizures, and might even result in less fatigue and fractures. Darolutamide is also under study for M1 HS prostate cancer with the ARAS-ENS trial, as noted earlier in this article.

This interesting trial design compares ADT plus darolutamide plus 6 cycles of docetaxel vs ADT plus docetaxel plus placebo, and in 2022 reported an OS benefit of the triple therapy including darolutamide vs ADT plus docetaxel alone.

## Molecular Profiling and Novel Therapeutics

Current AUA and National Comprehensive Cancer Network® guidelines recommend germline and somatic testing for men with advanced prostate cancer. About 12% of men with M1 prostate cancer will harbor actionable germline mutations, and about 25% of men with CRPC will have actionable somatic mutations. Most common are BRCA, ATM, and CHEK2. In 2021, there are 3 new drugs approved to treat men with actionable mutations: olaparib (Lynparza®, AstraZeneca), rucaparib (Rubraca®, Clovis Oncology), and pembrolizumab (Keytruda®, Merck).<sup>13-16</sup> Rucaparib is a PARP inhibitor that is approved for patients who had BRCA1/2 alterations, in patients with disease progression after an androgen receptor signaling inhibitor and docetaxel. Olaparib offers a survival benefit (from the PROFOUND trial) for patients with homologous recombination repair mutations after progression of disease on an androgen receptor signaling inhibitor, and does not mandate prior receipt of docetaxel chemotherapy. Indications for olaparib include the following homologous recombination repair mutations: BRCA 1/2 ATM, CDK12, CHEK2, CHEK1, BARD1, BRIP1, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L. Pembrolizumab has an agnostic indication for all solid tumors that are tested positive for

microsatellite instability-high and tumor mutation burden >10.<sup>13-16</sup>

## Summary

The management of advanced prostate cancer continues to evolve in exciting and sometimes unexpected ways, and 2022 has brought further options to our patients, including abiraterone, enzalutamide, and apalutamide in newly diagnosed, HS M1 prostate cancer, as well as apalutamide, enzalutamide, and darolutamide for M0 CRPC. The personalized medicine era is upon us also with approval of 3 agents for patients with actionable germline or somatic mutations. Interested readers should review the latest AUA guidelines on this topic.<sup>32,33</sup> ■

1. Komura K, Sweeney CJ, Inamoto T, Ibuki N, Azuma H, Kantoff PW. Current treatment strategies for advanced prostate cancer. *Int J Urol*. 2018;25(3):220-231.
2. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med*. 2015;373(8):737-746.
3. James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet*. 2016;387(10024):1163-1177.
4. Kyriakopoulos CE, Chen YH, Carducci MA, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis randomized phase III E3805 CHAARTED Trial. *J Clin Oncol*. 2018;36(11):1080-1087.
5. James ND, de Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. *N Engl J Med*. 2017;377(4):338-351.
6. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2019;381(1):13-24.
7. Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. *N Engl J Med*. 2019;381(2):121-131.
8. Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. *J Clin Oncol*. 2019;37(32):2974-2986.
9. Crawford ED, Schellhammer PF, McLeod DG, et al. Androgen receptor targeted treatments of prostate cancer: 35 years of progress with antiandrogens. *J Urol*. 2018;200(5):956-966.
10. Chi KN, Chowdhury S, Bjartell A, et al. Apalutamide in patients with metastatic castration-sensitive prostate cancer: final survival analysis of the randomized, double-blind, phase III TITAN study. *J Clin Oncol*. 2021;39(20):2294-2303.
11. Fizazi K, Galceran JC, Foulon S, et al. LBA5\_PR PEACE 1. Presented at virtual ESMO Congress, September 16-21, 2021.

“The personalized medicine era is upon us also with approval of 3 agents for patients with actionable germline or somatic mutations.”

12. Smith MR, Hussain M, Saad F, et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. *N Engl J Med.* 2022;386(12):1132-1142.
13. Siebert AL, Szymaniak BM, Numan Y, Morgans AK. Genetically informed prostate cancer treatment for metastatic disease. *Urol Clin North Am.* 2021;48(3):365-371.
14. LeVeé A, Lin CY, Posadas E, et al. Clinical utility of olaparib in the treatment of metastatic castration-resistant prostate cancer: a review of current evidence and patient selection. *Onco Targets Ther.* 2021;14:4819-4832.
15. Abida W, Patnaik A, Campbell D, et al. Ruca-parib in men with metastatic castration-resistant prostate cancer harboring a BRCA1 or BRCA2 gene alteration. *J Clin Oncol.* 2020;38(32):3763-3772.
16. Antonarakis ES, Piulats JM, Gross-Goupil M, et al. Pembrolizumab for treatment-refractory metastatic castration-resistant prostate cancer: multicohort, open-label phase II KEYNOTE-199 study. *J Clin Oncol.* 2020;38(5):395-405.
17. Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet.* 2011;377(9768):813-822.
18. Handy CE, Antonarakis ES. Sipuleucel-T for the treatment of prostate cancer: novel insights and future directions. *Future Oncol.* 2018;14(10):907-917.
19. Schellhammer PF, Chodak G, Whitmore JB, Sims R, Frohlich MW, Kantoff PW. Lower baseline prostate-specific antigen is associated with a greater overall survival benefit from sipuleucel-T in the Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) trial. *Urology.* 2013;8(6):1297-1302.
20. Higano CS, Armstrong AJ, Sartor AO, et al. Real-world outcomes of sipuleucel-T treatment in PROCEED, a prospective registry of men with metastatic castration-resistant prostate cancer. *Cancer.* 2019;125(23):4172-4180.
21. Caffo O, Veccia A, Kinspergher S, Maines F. Abiraterone acetate and its use in the treatment of metastatic prostate cancer: a review. *Future Oncol.* 2018;14(5):431-442.
22. Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med.* 2017;377(4):352-360.
23. Scott LJ. Enzalutamide: a review in castration-resistant prostate cancer. *Drugs.* 2018;78(18):1913-1924.
24. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *N Engl J Med.* 2018;378(26):2465-2474.
25. Sternberg CN, Fizazi K, Saad F, et al. Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med.* 2020;382(23):2197-2206.
26. Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med.* 2018;378(15):1408-1418.
27. Antonarakis ES, Lu C, Wang H, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. *N Engl J Med.* 2014;371(11):1028-1038.
28. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med.* 2013;369(3):213-223.
29. Mizokami A, Kimura G, Fujii Y, Hinotsu S, Izumi K. Considering bone health in the treatment of prostate cancer bone metastasis based on the results of the ERA-223 trial. *Int J Clin Oncol.* 2019;24(12):1629-1631.
30. Fizazi K, Shore N, Tammela TL, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med.* 2019;380(13):1235-1246.
31. Fizazi K, Shore N, Tammela TL, et al. Non-metastatic, castration-resistant prostate cancer and survival with darolutamide. *N Engl J Med.* 2020;383(11):1040-1049.
32. Lowrance WT, Breau RH, Chou R, et al. Advanced prostate cancer: AUA/ASTRO/SUO guideline PART I. *J Urol.* 2021;205(1):14-21.
33. Lowrance WT, Breau RH, Chou R, et al. Advanced prostate cancer: AUA/ASTRO/SUO guideline PART II. *J Urol.* 2021;205(1):22-29.

## AUA2022 COURSE

# Genetic Testing in Prostate Cancer: Understanding Clinical Implications for Early Detection and Management of Localized and Advanced Disease

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## Learning Objective

*At the conclusion of the activity, participants will be able to counsel men with BRCA1/2 mutations, Lynch syndrome, and other key inherited syndromes regarding their prostate cancer risk, and utilize genetic testing results to improve outcomes for patients with metastatic prostate cancer.*

## Introduction

Our understanding of germline mutations as an important cause of aggres-

sive prostate cancer has dramatically increased in recent years. Urologists treating men with prostate cancer are incorporating germline genetics into routine prostate cancer care, from early detection to management of men with localized or metastatic prostate cancer. Multiple organizations now provide guidance to aid in the appropriate use of genetic testing, but significant work remains in order to bring appropriate genetic testing into clinical practice.

## Hereditary and Familial Prostate Cancer

Family history is a critical consideration for prostate cancer risk. Men with a family history of prostate cancer have a higher incidence of prostate cancer and

higher prostate cancer specific mortality (compared to men without a family history of prostate cancer).<sup>1</sup> Men with a family history of prostate, breast, ovarian, or pancreatic cancer have a significantly higher risk of developing prostate cancer than men without a family history of these cancers. Interestingly, family history is an independent risk factor for developing prostate cancer, even when accounting for known genetic changes. This is perhaps related to social and environmental factors, but also could be related to currently unknown genetic factors. Thus, familial prostate cancer is a broad term that encompasses 15%-20% of cases and can include those patients with a strong family history of prostate cancer

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“Interestingly, family history is an independent risk factor for developing prostate cancer, even when accounting for known genetic changes.”

but no detectable genetic mutations. Hereditary prostate cancer, however, is estimated to account for 5%-10% of prostate cancer cases. These are generally due to higher penetrance inherited rare pathogenic mutations, such as mutations in *BRCA1*, *BRCA2*, or *ATM*, and these variants can greatly increase lifetime risk of developing prostate cancer. In addition to family history and rare pathogenic mutations, a third independent risk factor relates to single nucleotide polymorphisms which may or may not themselves have a functional role in increasing the risk of developing prostate cancer.<sup>2</sup> These smaller genetic changes are often grouped together to create genetic risk scores that can similarly inform prostate cancer risk.

## Germline Alterations

A number of rare pathogenic mutations have been implicated in heritable prostate cancer, most of which have important roles in the DNA damage repair machinery. These include *BRCA1*, *BRCA2*, *CHEK2*, *ATM*, and *PALB2*, along with mismatch repair (MMR) mutations responsible for Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, and *PMS2*). *BRCA1* and *BRCA2* are critical proteins in the process of homologous recombination, and pathogenic mutations in these genes have long been known to increase the risk of breast and ovarian cancers in women. Germline *BRCA1* and *BRCA2* mutations in men are associated with a significant increase in the risk of prostate cancer, and men with pathogenic *BRCA2* mutations are typically diagnosed at a younger age, have higher Gleason grade tumors, and have a shorter median survival time than men with sporadic prostate cancers.<sup>3,4</sup>

Several options for germline genetic

testing are now available for those men with prostate cancer who meet clinical guidelines (eg, National Comprehensive Cancer Network®) for germline testing. While single-gene testing, such as for *BRCA1* or *BRCA2*, can be performed, multigene panel testing has become more commonplace in the absence of a known familial mutation. These tests include a panel of genes associated with the disease of interest. For prostate cancer, these panels typically include *BRCA1*, *BRCA2*, *ATM*, *CHEK2*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, and *TP53* among others specific to the individual platform. Importantly, while many of the genes included in these panels have a clear association with prostate cancer risk, others carry a still unknown clinical significance with poorly defined cancer risk. Particular caution should be taken before performing a test that includes >20-30 genes, as these often includes genes without confirmed relevance to prostate cancer risk.

Before performing testing, patients should understand the possible testing results and the potential impact on themselves and family members. For example, many variants identified on multigene panel testing may not be clinically relevant. Some are known to be nonpathogenic, while others are indeterminate and classified as variants

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of uncertain significance. This occurs when a genetic change is present that differs from a normal control but there is insufficient information to classify it as deleterious or benign with respect to cancer risk. The possibility of a variant of uncertain significance, or “gray area,” result should be discussed up-front before any testing is performed.

## Guideline Statements on Testing and Early Detection

In recognizing the importance of germline mutations, National Comprehensive Cancer Network guidelines now distinguish indications according to tumor characteristics vs family/ancestry indications. Tumor-specific indications include: metastatic prostate cancer, high-/very high-risk prostate cancer, or intraductal/criform histology. Family history characteristics include 1 or more close blood relative with: breast cancer diagnosed at ≤50 years of age; ovarian cancer; pancreatic cancer; or metastatic, intraductal/criform, or high-/very high-risk prostate cancer. Additional indications include 2 or more relatives with breast or prostate cancer (any grade), or individuals with Ashkenazi Jewish ancestry.

In terms of early detection for men without a diagnosis of prostate cancer, current guidelines suggest that men with germline mutations that increase the risk of prostate cancer undergo prostate cancer screening starting at age 40 after a risk and benefit discussion. These guidelines recommend biopsy for PSA >3 ng/ml or for suspicious examination in these high-risk men. Furthermore, the guidelines suggest followup based upon initial PSA level for those whose initial screening does not trigger a biopsy. However, there is a need to better define the early detection approach for these high-risk men.

The role for dedicated and early screening in men with known or potential germline mutations predisposing to prostate cancer is being evaluated in a number of settings, including the IMPACT and PROFILE trials in the UK.<sup>5,6</sup> At the University of Michigan

**Table.** Select ongoing trials with relevance to DNA damage repair deficiency

Phase	Agent	Short Name	ClinicalTrials.gov
III	Rucaparib (mCRPC)	TRITON3	NCT02975934
III	Niraparib+Abiraterone+Pred vs Abi+Pred (mCSPC)	AMPLITUDE	NCT04497844
II	Docetaxel+carboplatin maintenance rucaparib	PLATIPARP	NCT03442556
II	Neoadjuvant niraparib		NCT04030559
III	Talazoparib+enza or talazoparib+placebo (mCSPC)	TALAPRO-3	NCT04821622
II	Durvalumab+olaparib (BCR)		NCT03148795
II	Olaparib (BCR)	BRCAaway	NCT03012321

BCR, biochemical recurrence. mCRPC, metastatic castration-resistant prostate cancer. mCSPC, metastatic castration-sensitive prostate cancer.

“In terms of early detection for men without a diagnosis of prostate cancer, current guidelines suggest that men with germline mutations that increase the risk of prostate cancer undergo prostate cancer screening starting at age 40 after a risk and benefit discussion.”

Prostate Cancer Risk Clinic, men who are known carriers of germline pathogenic mutations related to prostate cancer (eg *BRCA1/2*) are offered PSA screening and digital rectal examination starting at age 35, with a low PSA threshold for biopsy. PSA thresholds are set at 2 ng/ml for men under 50 years old and 2.5 ng/ml for men 50 years and over.<sup>7</sup> This is combined with additional urine biomarker testing with the objective of better defining the role for intensified risk-based prostate cancer screening in the United States. Another open study out of the National Cancer Institute utilizes a similar algorithm but also adds multiparametric MRI (NCT03805919).

## Treatment Implications

Men with *BRCA2* mutations have been shown in multiple studies to be at risk for more aggressive prostate cancer, with decreased survival rates compared to patients with sporadic prostate cancer. Key questions regarding eligibility of active surveillance in low-risk disease or treatment intensification in men with high-risk localized disease remain to be answered. In the metastatic setting, there is emerging evidence of the efficacy of PARP (poly[adenosine diphosphate {ADP}-ribose] polymerase) inhibitors and platinum-based chemotherapy in patients with germline and/or somatic biallelic defects in DNA repair genes. In the TOPARP-A trial, which led to U.S. Food and Drug Administration (FDA) breakthrough designation for olaparib in metastatic castration-resistant prostate cancer, having a DNA damage repair alteration appeared to predict response to olaparib.<sup>8</sup> This is particularly relevant in the context of the work by Pritchard and colleagues, finding germline DNA damage repair mutations in 11.8% of men with metastatic prostate cancer.<sup>9</sup> Further evidence for the Phase 3 PROFOUND trial demonstrated the efficacy of olaparib in metastatic castration-resistant prostate cancer patients with a mutation in *BRCA1*, *BRCA2*, or *ATM*, leading to FDA approval in this setting.<sup>10</sup> Additionally, in the single-arm TRITON2 trial, the large proportion of men with germline or somatic alterations in *BRCA1* or *BRCA2* who responded to rucaparib led to its ap-

proval in *BRCA1* and *BRCA2* mutated metastatic castration-resistant prostate cancer, as well.<sup>11</sup>

There is also evidence of increased sensitivity to platinum-based chemotherapy in metastatic prostate cancer patients with germline DNA repair mutations, likely related to the mechanism of action through DNA damage.<sup>12</sup> Due to the treatment implications, potential relevance for family members along with inconsistent insurance coverage and access to services, studies are ongoing to explore novel methods of delivering cancer genetic testing and counseling to men with metastatic prostate cancer. One of these is the University of Washington/Fred Hutch Cancer Center web-based GENTleMEN study (ClinicalTrials.gov, NCT03503097). There are also a number of ongoing therapeutic trials in this space (see Table).

Finally, there is also evidence across multiple different cancers that patients with increased tumor mutational burden, such as those with DNA MMR deficient tumors, are particularly sensitive to immune checkpoint inhibition. This is most commonly seen in colorectal cancer, which is the most common malignancy associated with Lynch syndrome. However, as mentioned above, mutations in MMR genes are also associated with prostate cancer and are likely present in approximately 5% of advanced prostate cancers.<sup>13</sup> The emerging data regarding MMR deficiency and checkpoint inhibition sensitivity have led to an FDA approval for pembrolizumab, a PD-1 inhibitor, in solid tumors with MMR deficiency such as in Lynch syndrome.<sup>14</sup> While there are still only limited data surrounding PD-1 sensitivity in MMR-deficient prostate cancer, there are reports of extreme responses to pembrolizumab in this setting.

## Conclusion

Germline mutations predisposing to prostate cancer have an increasing impact on the clinical management of prostate cancer—from pre-diagnosis genetic counseling, to screening and early detection, to newly diagnosed localized prostate cancer, and to metastatic disease. Utilizing platinum-based therapies,

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“Utilizing platinum-based therapies, immunotherapy, or PARP inhibitors in men with metastatic prostate cancer who have known germline mutations may lead to improved long-term outcomes, though additional research in these areas is needed.”

immunotherapy, or PARP inhibitors in men with metastatic prostate cancer who have known germline mutations may lead to improved long-term outcomes, though additional research in these areas is needed. Given emerging evidence

and guidelines, clinical pathways are now needed to facilitate germline testing in appropriately selected patients in order to inform treatment plans. Further work to improve access to genetic counseling, cancer screening, and treatment options for men with relevant germline mutations is likely to yield significant long-term benefits for these patients. ■

1. Liss MA, Chen H, Hemal S, et al. Impact of family history on prostate cancer mortality in White men undergoing prostate specific antigen based screening. *J Urol*. 2015;193(1):75-79.
2. Shi Z, Platz EA, Wei J, et al. Performance of three inherited risk measures for predicting prostate cancer incidence and mortality: a population-based prospective analysis. *Eur Urol*. 2021;79(3):419-426.
3. Castro E, Goh C, Leongamornlert D, et al. Effect of BRCA mutations on metastatic relapse and cause-specific survival after radical treatment for localised prostate cancer. *Eur Urol*. 2015;68(2):186-193.
4. Tryggvadottir L, Vidarsdottir L, Thorgeirsson T, et al. Prostate cancer progression and survival in BRCA2 mutation carriers. *J Natl Cancer Inst*. 2007;99(12):929-935.
5. Page EC, Bancroft EK, Brook MN, et al. Interim results from the IMPACT study: evidence for prostate-specific antigen screening in BRCA2 mutation carriers. *Eur Urol*. 2019;76(6):831-842.
6. Castro E, Mikropoulos C, Bancroft EK, et al. The PROFILE feasibility study: targeted screening of men with a family history of prostate cancer. *Oncologist*. 2016;21(6):716-722.
7. Sessine MS, Das S, Park B, et al. Initial findings from a high genetic risk prostate cancer clinic. *Urology*. 2021;156:96-103.
8. Mateo J, Carreira S, Sandhu S, et al. DNA-repair defects and olaparib in metastatic prostate cancer. *N Engl J Med*. 2015;373(18):1697-1708.
9. Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *N Engl J Med*. 2016;375(5):443-453.
10. Hussain M, Mateo J, Fizazi K, et al. Survival with olaparib in metastatic castration-resistant prostate cancer. *N Engl J Med*. 2020;383(24):2345-2357.
11. Abida W, Patnaik A, Campbell D, et al. Rucaparib in men with metastatic castration-resistant prostate cancer harboring a BRCA1 or BRCA2 gene alteration. *J Clin Oncol*. 2020;38(32):3763-3772.
12. Cheng HH, Pritchard CC, Boyd T, Nelson PS, Montgomery B. Biallelic inactivation of BRCA2 in platinum-sensitive metastatic castration-resistant prostate cancer. *Eur Urol*. 2016;69(6):992-995.
13. Grindedal EM, Møller P, Eeles R, et al. Germ-line mutations in mismatch repair genes associated with prostate cancer. *Cancer Epidemiol Biomarkers Prev*. 2009;18(9):2460-2467.
14. Boyiadzis MM, Kirkwood JM, Marshall JL, Pritchard CC, Azad NS, Gulley JL. Significance and implications of FDA approval of pembrolizumab for biomarker-defined disease. *J Immunother Cancer*. 2018;6(1):35.

## AUA2022 COURSE

# Incorporating Genomic Testing for Prostate Cancer into Your Practice

Joseph Wagner, MD

Author, Course Director

Matthew Cooperberg, MD, MPH

Panelist

Daniel Lin, MD

Panelist

## Learning Objective

*At the conclusion of the activity, participants will be able to describe which molecular tests can be performed on prostatectomy specimens and differentiate between somatic and germline mutations.*

Mounting evidence suggests genomic tests are useful through all stages of prostate cancer diagnosis and treatment. “Incorporating Genomic Testing for Prostate Cancer into Your Practice” was selected as an Instructional Course

for AUA2022 held in New Orleans. Led by course director Joseph Wagner, MD and a superb faculty comprised of Matthew Cooperberg, MD and Daniel Lin, MD, this course utilized an index case and a flipped classroom format to encourage participant engagement. The course focused on identifying a patient’s unique clinical characteristics, assessing prognostic endpoints, and reviewing American Urological Association and National Comprehensive Cancer Network® guidelines for genomic testing for prostate cancer.

A brief review demonstrates the pathway of DNA to RNA to proteins. Examples of tests examining each of these in the prostate cancer arena are given. The definition of germline and somatic mutations is explained (somatic mutations occur in a single body cell and cannot be inherited; germline

mutations occur in gametes and can be passed into offspring). Studies demonstrating the high rates of upgrading/downgrading and upstaging/downstaging, and thereby the need for better prognostic tests, are discussed.

The index patient presents to his urologist with an elevated PSA. Stressing a shared decision-making process, prostate biopsy, MRI, surveillance, and molecular/genomic testing (4K, PHI, Select MDx, ExoDX™, etc) are all presented and a plan implemented. This process can be repeated for a negative biopsy with the addition of other tissue-based genomic tests performed on the biopsy material (Confirm MDx, etc). Our index patient is diagnosed with prostate cancer and chooses to utilize genomic testing to help him make

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“The availability and marketing of genomic testing has outpaced a deliberate, evidence-based medicine approach to using these tests.”

a treatment decision and settles on surgery. Though he has a family history of prostate cancer, he does not meet the criteria for germline testing.<sup>1</sup> Unfortunately, his pathology specimen shows several adverse features. After discussing the 2 commercially available genomic tests that can be performed on prostatectomy specimens (Prolaris® and Decipher), he has genomic testing performed on the pathological specimen and is found to have a high risk of recurrence for which adjuvant or early salvage radiation has been shown to be advantageous over standard salvage radiation therapy.<sup>2</sup>

According to Joseph R. Wagner, MD, director of robotic surgery at Hartford Healthcare and chairman of the Department of Urology at Hartford Hospital in Connecticut, multiple genomic tests for men considering a prostate biopsy and at all stages of prostate cancer can aid in making different treatment decisions. Germline testing results can also influence a patient’s treatment options. For instance, a patient with a BRCA2 mutation is at higher risk for progression and may have a lower threshold for definitive therapy than a patient without a similar mutation. Furthermore, the family members of such a patient, both male and female, can consider testing.

“Genomic testing can dramatically influence the treatment of prostate cancer. A patient might migrate away from a prostate biopsy to continued monitoring of his PSA and be spared the diagnosis of a clinically insignificant prostate cancer. He may choose active surveillance over definitive therapy

based on the result of genomic testing,” Dr. Wagner said. “His genomic test may aid his radiation oncologist concerning the need for concurrent androgen deprivation therapy with his radiation. Genomic testing can help a patient decide whether to pursue adjuvant or early salvage treatment. Clearly, the influence of genomic testing is significant.”

The availability and marketing of genomic testing has outpaced a deliberate, evidence-based medicine approach to using these tests. Multiple seminal validation studies used in the approval of genomic tests are presented and underscore their importance in prostate cancer detection and treatment decision making. The utilization of PARP inhibitors to treat castrate resistant metastatic prostate cancer in men with germline BRCA2 mutations is an excellent example of the rapidly evolving field of precision medicine based on genomic testing results. Although not all patients require such tests, they can be useful depending on the clinical circumstances, according to Dr. Wagner.

In determining which patients to test, the first step for doctors should be to familiarize themselves with National Comprehensive Cancer Network/American Urological Association guidelines and the genomic tests that are available, according to Dr. Wagner. All the tests have different clinical end-

“The utilization of PARP inhibitors to treat castrate resistant metastatic prostate cancer in men with germline BRCA2 mutations is an excellent example of the rapidly evolving field of precision medicine based on genomic testing results.”

“Continued medical education is crucial to help urologists stay current in this rapidly changing field.”

points and utilities; therefore, it is important to understand the characteristics of each to determine which patients are appropriate for genomic testing. It is with this kind of understanding that the doctor and patient can participate in shared decision making.<sup>3</sup>

“Personally, I prefer to explain the nuances of the various tests and help the patient decide which is best for him. For instance, if a patient is deciding between active surveillance and definitive treatment, the clinical outcome of one test compared to another might be more appealing to him as he makes a challenging decision,” Dr. Wagner said.

DNA, RNA, and proteins are responsible for the current parameters (PSA, Grade Group, etc) used to determine the clinical significance of prostate cancer. It stands to reason that adding genomic tests which directly examine DNA/RNA/proteins will enhance the prognostic utility of these traditional parameters. Continued medical education is crucial to help urologists stay current in this rapidly changing field.

## Acknowledgment

We thank Tara McLaughlin, PhD for her help with reviewing the article. ■

1. Giri VN, Knudsen KE, Kelly WK, et al. Implementation of germline testing for prostate cancer. Philadelphia Prostate Cancer Consensus Conference 2019. *J Clin Oncol*. 2020;38(24):2798-2811.
2. Lokeshwar SD, Syed JS, Segal D, Rahman SN, Sprenkle PC. Optimal use of tumor-based molecular assays for localized prostate cancer. *Curr Oncol Rep*. 2022;24(2):249-256.
3. Alam S, Tortora J, Staff I, McLaughlin T, Wagner J. Prostate cancer genomics: comparing results from three molecular assays. *Can J Urol*. 2019;26(3):9758-9762.

AUA2022 PRESENTATION

# Urological Care for the Advanced Practice Provider Program. Prostate Cancer Biomarkers: What to Choose and When to Use

Rachel Hastings, MS, PA-C  
*Author, Presenter*

## Learning Objective

*At the conclusion of the activity, participants will be able to identify biomarkers used for initial diagnosis, risk stratification, posttreatment, and advanced disease.*

## Introduction

In recent years we have seen great strides in the diagnosis and treatment of prostate cancer. As we look to the future, we hope to decrease overdiagnosis and treatment of insignificant cancer, improve detection of clinically significant disease, and further risk stratify patients for appropriate treatment by incorporating the use of biomarkers and new imaging studies.

Until now, PSA has had the greatest impact on diagnosis as well as management, but PSA lacks specificity and relying on PSA alone has been proven to lead to overdiagnosis and overtreatment while still missing significant disease.<sup>1</sup> Although we have risk stratification tools and risk calculators incorporating Gleason score/grade and clinical stage,

many prostate cancers are multifocal, and may carry a remarkable amount of heterogeneity within or between tumor foci.<sup>2</sup> Novel imaging studies and biomarkers will help at all stages of our clinical pathway from initial screening to risk stratification of localized disease as well as serve as prognostic indicators for posttreatment failures and advanced disease.

## Biomarker Characterization

A biomarker is a biological molecule that can be objectively measured and evaluated as a sign of a normal or abnormal biological process and pathogenic condition/disease. Currently, we have both urine and blood-based biomarkers for initial screening. There are tissue-based biomarkers available for assessment of treatment escalation or de-escalation following diagnosis, as well as circulating tumor tests and imaging tests for ongoing surveillance. All of these tests are increasingly incorporated into our clinical care paradigm, but how can we use them most effectively?

## Biomarkers for Screening and Early Detection

PSA limitations drive our need for more tools aimed at reducing unnecessary biopsies without sacrificing early detection of clinically significant prostate cancer.

In this space, we have both urine- and blood-based biomarkers. These markers help guide screening and detection of clinically significant prostate cancer (Table 1).<sup>3-8</sup>

## Biomarkers for Repeat Biopsy

Biomarkers and imaging studies that help guide decision making regarding repeat biopsy include MRI, Confirm-MDX, PCA3, MyProstateScore, Prostate Health Index, and 4K (Table 2).

As Tables 1 and 2 illustrate, biomarkers in these spaces perform similarly and our choice depends on need, cost, convenience (home vs nursing visit vs provider visit), and patient and practitioner preference. Considerations also

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**Table 1.** Biomarkers for screening and early detection

Test	Source	Components	NPV	Notes
PSA	Blood			Lacks specificity; can also use fPSA, PSA, DT
PHI	Blood	ProPSA and free PSA	94%	Reduces unnecessary biopsy; active surveillance monitoring; prediction of csPCa
4K	Blood	PSA, fPSA, and human kallikrein 2 along with clinical factors	96%	Reduces unnecessary biopsy; Probability (0%–100%) of csPCa on biopsy
SelectMDx	Urine (post-DRE)	Gene panel along with clinical factors	95% for GG2; 99% for GG4 and greater	
ExoDx™	Urine	Gene panel of exosomal RNA (ERG, PCA3, and SPDEF)	95% for GG2; 97% for GG3 and greater	No DRE or clinical factors but does need to be first void; improved identification of high-grade disease

csPCa, clinically significant prostate cancer. DRE, digital rectal examination. DT, doubling time. fPSA, free PSA. GG, Grade Group. MDx, SelectMDx. PHI, Prostate Health Index.

**Table 2.** Biomarkers for repeat biopsy

Test	Source	Components	NPV	Notes
ConfirmMDX	Tissue	Hypermethylation of GSTP1, APC and RASSF1	95%	Evaluates for field effect on biopsy
PCA3	Urine (post-DRE)	Non-coding mRNA		No correlate with PSA or prostate volume
MPS	Urine (post-DRE)	PCA3 and T2:ERG	98%	Score from 0-11 grouped into low, intermediate, and high categories; prediction for risk of PCa and csPCa
PHI	Blood	ProPSA and free PSA	94%	Creates composite score to indicate likelihood of PCa
4K	Blood	Free PSA, total PSA and human kallikrein 2 along with clinical factors	96%	Probability (0%-100%) of csPCa on biopsy

csPCa=clinically significant prostate cancer. DRE=digital rectal examination. MPS=MyProstateScore. PCa=prostate cancer. PHI=Prostate Health Index.

“PSA limitations drive our need for more tools aimed at reducing unnecessary biopsies without sacrificing early detection of clinically significant prostate cancer.”

include lacking head-to-head studies, interpretation variability based on cutoff values and patient/clinician education, evaluation when on a 5-alpha reductase inhibitors, and validation of translation to improved outcomes. National Comprehensive Cancer Network® (NCCN®) and American Urological Association guidelines do not recommend these tests as first-line screening but state they may be used for patients who require further delineation of risk.<sup>9</sup>

## Biomarkers for Risk Stratification

For patients with localized prostate cancer, current risk stratification methods include PSA kinetics/levels, Gleason score and nomograms/models (Memorial Sloan Kettering Cancer Center, Cancer of the Prostate Risk Assessment), but as we lean further into the space of personalized medicine, genomics may have the potential to further or more accurately delineate risk. This input can potentially impact treat-

ment decision making as well as oncologic outcomes.

In the pretreatment space we have tissue-based biomarkers to help patients decide between active surveillance and treatment, as well as those who may benefit from treatment escalation, ie the addition of androgen deprivation therapy to radiation (Table 3).

These biomarkers can help guide short-term surveillance/treatment, but studies are still ongoing regarding the long-term oncologic benefit. We have seen promise not only in regard to survival but in minimizing treatment related side effects, and this becomes increasingly important as our patients are at younger ages at diagnosis and treatment. Ultimately, the overall clinical picture is more important than any 1 test. Prostate cancer is known to be multifocal as well as heterogeneous. These tissue-based biomarkers sample the

highest volume and Grade Group (GG) of disease, but that may not necessarily correlate to the foci that have the most potential for disease progression. Therefore, these results certainly are helpful but likely incomplete.

Tissue-based biomarkers are ideally suited for low and favorable intermediate-risk patients following biopsy and post-radical prostatectomy (RP) patients with pT2 positive margins, pT3, and/or rising PSAs. As experience grows, these tests are increasingly being incorporated into treatment guidelines as they are proving to be beneficial in risk stratification.<sup>11-17</sup>

## Imaging

Currently MRI plays an important role in initial screening (who to biopsy) and

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**Table 3.** Biomarkers for risk stratification

Name	Methodology	Indications	Reported Outcomes
Prolaris	31 Cell cycle genes	Pretreatment post-RP	Reported on 10-point scale; gives a score % within the patient's NCCN risk group while providing % risk of 10-yr disease specific mortality and distant mets
Decipher	22 RNA markers	Pretreatment post-RP	Independent of clinical and demographic data; provides % risk of distant metastases in 5, 10 yrs; 15-yr disease specific mortality; risk of adverse pathology at RP
Oncotype	12 Cancer genes over 4 different pathways	Pretreatment	Numerical score combined with NCCN risk groupings to report comprehensive risk score shown as a % risk of prostate cancer death within 10 yrs, metastasis within 10 yrs and risk of adverse pathology on RP

RP, radical prostatectomy.

active surveillance, as well as monitoring/screening for metastatic disease. MRI allows for a more accurate, targeted biopsy, a practice proven to increase detection of GG2 or greater, but limitations or barriers include negative predictive value (NPV) variation between both radiologists and centers, time, cost, and accessibility. More data are needed on how to integrate biomarkers with MRI.<sup>18</sup>

Prostate-specific membrane antigen positron emission tomography can be used for initial staging of high-risk disease as well as for biochemical recurrence and for metastatic disease monitoring. Many patients who were M0 by traditional imaging modalities will now be M1. It remains unclear, however, how this will change our treatment paradigms and whether it will ultimately lead to improved outcomes.

As prostate-specific membrane antigen positron emission tomography is incorporated into our clinical pathway, we must remember to integrate the entire clinical picture into our decision making as we again see sensitivity variation dependent on PSA, variability between centers, false positives, etc.<sup>19,20</sup>

## Biomarkers for Post-Operation/Treatment

Just as in the pretreatment setting, tissue-based tests such as Prolaris, Oncotype and Decipher as well as imaging studies can have a valuable role in the management of patients following primary treatment (Table 3). In the post-treatment setting, these tests are useful for guiding posttreatment surveillance as well as initiation of adjuvant/salvage treatments.<sup>13-17</sup>

## Biomarkers for Advanced Disease

It is imperative to get an accurate and detailed history on prostate cancer patients as many may qualify for germline testing. Germline testing is recommended for all patients with metastatic disease and should be considered for patients with localized/regional disease but increased risk factors (strong family history, intraductal/criform). It has become known that up to 20% of these

patients will have unique treatment options based on the testing such as PARP inhibitor or immune checkpoint inhibitor.<sup>21</sup>

In addition, there has been recent robust interest in emerging biomarkers such as circulating tumor cells for castrate-resistant prostate cancer.

## Conclusion

Further characterization of prostate cancer is increasingly important as we strive for more personalized care for our patients. Selection of appropriate biomarkers can be highly nuanced and must be dependent on the clinical picture. Given the complex and heterogenous nature of prostate cancer, 1 biomarker cannot answer all our questions. As always, more research on incorporating our current biomarkers as well as new research is needed. It is important to incorporate these tests into your practice and engage in clinical trials when available. In the early detection pathways, focus is on how these tests can be used with imaging studies and how they perform in diverse populations. Further studies will help guide how to implement our tissue-based tests to aid in treatment decisions for active surveillance or stratification/treatment of intermediate-risk disease. We have seen tremendous recent growth in utilization and development of biomarkers, imaging, and germline testing in the post-primary treatment setting, and as more studies emerge we will further our ability to stratify patients requiring treatment escalation and tailor more personalized treatment options. In the future, biomarkers will continue to enhance our ability to diagnosis and treat patients with prostate cancer above and beyond our current standard diagnostic and prognostic tools. ■

1. Thompson IM, Ankerst DP, Chi C, et al. Operating characteristics of prostate specific antigen in men with an initial PSA level of 3.0 ng/ml or lower. *JAMA*. 2005;294(1):66-70.
2. Løv M, Zhao S, Axcrone U, et al. Multifocal primary prostate cancer exhibits high degree of genomic heterogeneity. *Eur Urol*. 2019;75(3):498-505.
3. Parekh DJ, Punnen S, Sjöberg DD, et al. A multi-institutional prospective trial in the USA confirms that the 4K score accurately identifies men with high grade prostate cancer. *Eur Urol*. 2015;68(3):464-470.
4. Kim JH, Hong SK. Clinical utility of current biomarkers for prostate cancer detection. *Investig Clin Urol*. 2021;62(1):1-13.

5. Loeb S, Sanda MG, Broyles DL, et al. The prostate health index selectively identifies clinically significant prostate cancer. *J Urol*. 2015;193(4):1163-1169.
6. Haese A, Trooskens G, Steyaert S, et al. Multi-center optimization and validation of a 2-gene mRNA urine test for detection of clinically significant prostate cancer before initial prostate biopsy. *J Urol*. 2019;202(2):256-263.
7. Margolis E, Brown G, Partin A, et al. Predicting high-grade prostate cancer at initial biopsy: clinical performance of the ExoDx (EPI) prostate intelliscore test in three independent prospective studies. *Prostate Cancer Prostatic Dis*. 2022;25(2):296-301.
8. McKiernan J, Noerholm M, Tadiogola V, et al. A urine-based exosomal gene expression test stratifies risk of high-grade prostate cancer in men with prior negative prostate biopsy undergoing repeat biopsy. *BMC Urol*. 2020;20(1):138.
9. NCC Network. Prostate cancer early detection guidelines; Available at <https://www.nccn.org/guidelines/guidelines-detail?category=2&id=1460>.
10. Sathianathan NJ, Kuntz KM, Alarid-Escudero F, et al. Incorporating biomarkers into the primary prostate biopsy setting: a cost-effectiveness analysis. *J Urol*. 2018;200(6):1215-1220.
11. Kim HL, Li P, Huang HC, et al. Validation of the decipher test for predicting adverse pathology in candidates for prostate cancer active surveillance. *Prostate Cancer Prostatic Dis*. 2019;22(3):399-405.
12. Herlemann A, Huang HC, Alam R, et al. Decipher identifies men with otherwise clinically favorable-intermediate risk disease who may not be good candidates for active surveillance. *Prostate Cancer Prostatic Dis*. 2020;23(1):136-143.
13. Jairath NK, Dal Pra A, Vince R, et al. A systematic review of the evidence for the decipher genomic classifier in prostate cancer. *Eur Urol*. 2021;79(3):374-383.
14. Ross AE, Feng FY, Ghadessi M, et al. A genomic classifier predicting metastatic disease progression in men with biochemical recurrence after prostatectomy. *Prostate Cancer Prostatic Dis*. 2014;17(1):64-69.
15. Freedland SJ, Choerung V, Howard L, et al. Utilization of a genomic classifier for prediction of metastasis following salvage radiation therapy after radical prostatectomy. *Eur Urol*. 2016;70(4):588-596.
16. Klein EA, Cooperberg MR, Magi-Galluzzi C, et al. A 17-gene assay to predict prostate cancer aggressiveness in the context of Gleason grade heterogeneity, tumor multifocality, and biopsy undersampling. *Eur Urol*. 2014;66(3):550-560.
17. Van Den Eeden SK, Lu R, Zhang N, et al. A biopsy-based 17-gene genomic prostate score as a predictor of metastases and prostate cancer death in surgically treated men with clinically localized disease. *Eur Urol*. 2018;73(1):129-138.
18. Westphalen AC, McCulloch CE, Anaokar JM, et al. Variability of the positive predictive value of PI-RADS for prostate MRI across 26 centers: experience of the Society of Abdominal Radiology Prostate Cancer Disease-focused panel. *Radiology*. 2020;296(1):76-84.
19. Sonni I, Eiber M, Fendler WP, et al. Impact of <sup>68</sup>Ga-PSMA-11 PET/CT on staging and management of prostate cancer patients in various clinical settings: a prospective single-center study. *J Nucl Med*. 2020;61(8):1153-1160.
20. Fendler WP, Ferdinandus J, Czernin J, et al. Impact of <sup>68</sup>Ga-PSMA-11 PET on the management of recurrent prostate cancer in a prospective single-arm clinical trial. *J Nucl Med*. 2020;61(12):1793-1799.
21. Thoma C. Targeting DNA repair defects in prostate cancer. *Nat Rev Urol*. 2020;17(8):432.



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### *Acknowledgements:*

*This educational activity is supported by independent educational grants from Astellas, AstraZeneca, Bayer HealthCare Pharmaceuticals Inc., Exact Sciences Corporation, Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC, Lantheus Medical Imaging, Pfizer, Inc., and Sanofi Genzyme.*

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