American Urological Association

AUANews

THE OFFICIAL NEWSMAGAZINE OF THE AMERICAN UROLOGICAL ASSOCIATION

2021 AUA Annual Meeting Highlights: Prostate Cancer

Features highlights from the following AUA 2021 Annual Meeting sessions:

- AUA Guidelines on Advanced/Metastatic/ Castration Resistant Prostate Cancer
- State-of-the-Art Lecture: Personalized Medicine in the Management of Prostate Cancer Across the Patient Care Continuum
- Incorporating Genomic Testing for Prostate Cancer into Your Practice
- Genetic Testing in Prostate Cancer: Understanding Clinical Implications for Early Detection, Localized Disease and Castration Resistant Prostate Cancer
- Common Dilemmas in Prostate Cancer Detection and Management
- What's New in the Management of Hormone Naïve and Castrate Resistant Prostate Cancer: A Case-Based Session for Urologists, Advanced Practice Providers and Team
- Urologic Care for the Advanced Practice Provider: Advanced Prostate Cancer Management

INSIDE THIS ISSUE

ARTICLES

AUA*News* Editor
John D. Denstedt, MD, FRCSC, FACS, FCAHS

Chair, Office of Education
Jay D. Raman, MD, FACS

Target Audience
Urologists, urologists in training and nonphysician providers involved in urology.

Acknowledgements
The AUA Office of Education thanks the companies who support continuing education of physicians. The AUA recognizes the following companies for providing educational grant support:

Amgen
Astellas
Exact Sciences Corporation
Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC
Pfizer, Inc.
Sanofi Genzyme

American Urological Association Education & Research, Inc. ensures that all educational activities are developed and implemented independent of the control and/or influence of any commercial interests (ACCME: SCS1).

CME Information

Method of Participation

To claim CME credit/hours of participation, the learner must read the content, complete the posttest, passing with 80% accuracy and submit the evaluation and credit request form by visiting https://auau.auanet.org/content/21HLPC

Estimated time to complete this activity: 1.25 hours
Release Date: December 2021
Expiration Date: December 31, 2022

Accreditation Statement

The American Urological Association (AUA) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Credit Designation

The American Urological Association designates this enduring material for a maximum of 1.25 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Other Learners

The AUA is not accredited to offer credit to participants who are not MDs or DOs. However, the AUA will issue documentation of participation that states that the activity was certified for *AMA PRA Category 1 Credit*™.

Evidence Based Content

It is the policy of the AUA to ensure that the content contained in this CME activity is valid, fair, balanced, scientifically rigorous, and free of commercial bias.

AUA Disclosure Policy

All persons in a position to control the content of an educational activity (i.e., activity planners, presenters, authors) are required to disclose to the provider all financial relationships with any commercial interest during the previous 24 months. The AUA must determine if the individual's relationships may influence the educational content and mitigate any conflicts of interest prior to the commencement of the educational activity. The intent of this disclosure is not to prevent individuals with relevant financial relationships from participating, but rather to provide learners information with which they can make their own judgments.

All disclosures for this activity may be viewed by visiting https://auau.auanet.org/content/21HLPC

Mitigation of Identified Conflict of Interest:

All disclosures will be reviewed by the AUA Conflict of Interest (COI) Review Work Group Chair and/or Vice Chair for identification of conflicts of interest. The AUA COI Review Work Group, working with Office of Education staff, will document the mechanism(s) for management and mitigation of the conflict of interest and final approval of the activity will be documented prior to implementation. Any of the mechanisms below can/will be used to mitigate conflict of interest:

- Peer review for valid, evidence-based content by the AUA COI Review Work Group.
- Attestation that clinical recommendations are evidence-based and free of commercial bias.
- Introduction of a debate format (point-counterpoint)
- Inclusion of moderated panel discussion with unbiased moderator
- Publication of a parallel or rebuttal article for an article that is felt to be biased
- Divestiture of the relationship by faculty
- Recusal from controlling relevant aspects of planning
- Selection of alternative faculty for specific topic

Off-label or Unapproved Use of Drugs or Devices

The audience is advised that this continuing medical education activity may contain reference(s) to off-label or unapproved uses of drugs or devices. Please consult the prescribing information for full disclosure of approved uses.

Disclaimer

The opinions and recommendations expressed by faculty, authors and other experts whose input is included in this program are their own and do not necessarily represent the viewpoint of the AUA.

Reproduction Permission

AUA2021 COURSE

AUA Guidelines on Advanced/Metastatic/Castration Resistant Prostate Cancer

Michael S. Cookson, MD, MMHC
Author, Course Director

Adam S. Kibel, MD
Panelist

David F. Jarrard, MD
Panelist

William L. Lowrance, MD
Panelist

Learning Objectives

At the conclusion of the activity, participants will be able to:

- *Identify the active agents and their mechanism of action in the management of nonmetastatic castration resistant prostate cancer (CRPC) and metastatic CRPC.*
- *Describe sequencing and indications for active treatment with approved agents in the management of nonmetatstic CRPC.*
- *Analyze the evidence and outcomes on the treatment of M0 and M1 CRPC as outlined in the newly updated AUA CRPC guidelines.*
- *Improve diagnostic and therapeutic decision-making processes by illustrating the application of these guidelines in urological practice.*
- *Analyze breakthrough treatments in the management of advanced and metastatic hormone naïve prostate cancer.*

Improvements in the understanding of genetic alterations and their impact on men with advanced prostate cancer (APC), advances in precision medicine and refinements in diagnostic imaging were some of the highlights of this year's course. Consequently, the evaluation and treatment of men with advanced, metastatic, and castration resistant prostate cancer (CRPC) continues to evolve. This is important when considered in the context of a disease that results in the second leading cause of cancer deaths in men.[1] Improved overall survival (OS) with a multitude of different therapeutic agents and combinations, coupled with the success of earlier use of some already approved agents, have resulted in updates to these guidelines.

On one end of the spectrum within this disease state, treatment of men with metastatic CRPC (mCRPC) continues to evolve. In the past, once androgen deprivation therapy (ADT) failed, treatment of mCRPC was only palliative. However, landmark studies by Tannock[2] and Petrylak[3] et al demonstrated that docetaxel improved OS in patients with mCRPC compared to mitoxantrone. Since then, the field has evolved with an explosion of new therapies. Recently, a multitude of additional therapeutics (abiraterone, sipuleucel-T, cabazitaxel, enzalutamide and radium-223) have demonstrated survival benefit and been approved by the U.S. Food and Drug Administration (FDA) based on clinical trials in men with mCRPC.[4-9] Now, some of these agents and others discussed are showing benefit earlier in the disease state, including the metastatic hormone sensitive (mHSPC) and nonmetastatic (M0 CRPC) setting.

At the virtual AUA 2021 meeting, we presented the updated APC Guidelines. One reason for the continued updates is the rapid evolution of the field. While new agents are undergoing clinical trials, other agents are moving up in the sequencing. We included 3 trials in patients with M0 CRPC using androgen targeted therapy. These trials resulted in a significant delay in metastasis-free survival (MFS). The first published study was the SPARTAN trial, a randomized trial comparing apalutamide vs placebo in M0 CRPC at high risk for metastasis.[10] The investigators reported a highly significant improvement in MFS with use of apalutamide vs placebo in men at high risk for metastasis as determined by a prostate specific antigen doubling time of 10 months or less. This has resulted in the FDA approval of apalutamide for use in men with M0 CRPC. Using a similar trial design, results from PROSPER also demonstrated similar improvement in MFS in men with high risk M0 CRPC with use of enzalutamide.[11] A third study, ARAMIS, also demonstrated significant improvement in MFS in men with M0 CRPC using darolutamide as compared to placebo in high risk men with M0 CRPC.[12] In addition, the prolonged MFS and longer followup of these trials has resulted in positive OS outcomes.[13] This now provides further evidence for the early use of these novel second generation antiandrogen agents in patients with M0 CRPC in order to not only delay metastases but also to prolong OS. Finally, the impact of next generation positron emission tomography (PET) scan imaging will continue to better identify patients with small volume metastases and should result in reclassification of patients in this disease state.

The course included review of the management of men with biochemical recurrence after failed local therapy. The importance of risk stratification was discussed, including clinical factors such as time to biochemical failure and prostate specific antigen doubling time, tumor grade and stage, all of which may impact initiation of treatment. For the truly high-risk patients with biochemical recurrence after failed local therapy, initiation of ADT may be appropriate and, when applied, consideration to intermittent therapy was discussed.[14] Also discussed was the FDA approval of novel prostate-specific membrane antigen (PSMA) PET scans in the evaluation of high-risk patients for both staging and in the assessment of recurrent prostate cancer.[15,16] Both Gallium 68 PSMA-11 PET and ^{18}F-DCFPyL, or

→ Continued on page 4

PYLARIFY®, are now FDA approved and will be changing the way we stage and ultimately treat men with APC. The course also emphasized the importance of germline testing in men with newly diagnosed APC.

The incidence of germline mutations in genes mediating DNA-repair processes among men with metastatic prostate cancer was 11.8%.[17] Also discussed was the role of genetic counseling in these prior to the germline testing.

Among men with mHSPC, we highlighted guidance on the management of mHSPC. We reviewed the trials demonstrating OS benefit with the addition of docetaxel chemotherapy to ADT from both the CHAARTED and STAMPEDE trials.[18,19] In the CHAARTED trial, the benefit was most pronounced among men with "high volume" metastatic disease as predefined in the study. In addition to studies demonstrating the benefit of docetaxel chemotherapy, the addition of androgen targeted therapy to traditional luteinizing hormone-releasing hormone therapy resulted in significant improvement in OS when compared to luteinizing hormone-releasing hormone therapy alone. Both abiraterone acetate plus prednisone and enzalutamide or apalutamide when combined with conventional ADT demonstrated significant OS benefit in men with mHSPC. Collectively, these studies demonstrate that men with mHSPC should be offered ADT plus one of these novel androgen-axis therapies or docetaxel chemotherapy.

Management of patients with mCRPC was also reviewed. Enzalutamide before chemotherapy in men with asymptomatic or mildly symptomatic mCRPC was discussed.[9] The study demonstrated significant improvement in both OS and radiographic progression-free survival in patients treated with enzalutamide vs placebo. Previously, abiraterone plus prednisone was approved in the pre-chemotherapy setting as well.[4] In addition, the use of an alpha emitting radionuclide therapy was discussed relative to the FDA approved use of radium-223 dichloride in men with mCRPC who are symptomatic from bone metastases and without visceral metastatic disease.[8]

In patients with mCRPC who are asymptomatic or have minimal symptoms with metastases and have received no prior docetaxel, clinicians should offer abiraterone plus prednisone, enzalutamide, docetaxel or sipuleucel-T. In this instance, sipuleucel-T is appropriate and will not be recommended for more severe symptoms, making it an important consideration in this early asymptomatic or minimally symptomatic setting.

> "The treatment of APC is undergoing an evolution with multiple new agents on the horizon, from immune modulators to vaccines to novel antiandrogens."

Patients with symptomatic mCRPC, a good performance status and who have not previously received docetaxel are candidates for several approved agents. Clinicians should offer abiraterone plus prednisone, enzalutamide or docetaxel chemotherapy. For patients with symptomatic bone metastases and no visceral metastases, clinicians should offer radium-223. Amongst those with symptomatic mCRPC and prior docetaxel therapy with a good performance status, treatment with abiraterone + prednisone, cabazitaxel or enzalutamide should be offered. If the patient received abiraterone + prednisone or enzalutamide before docetaxel chemotherapy, they should be offered cabazitaxel. Patients with mCRPC with prior docetaxel treatment who are symptomatic with bone metastases and no visceral metastases should be offered radium-223.

One new area in this year's course is the development of precision-based therapy with a new class of agents, poly (ADP-ribose) polymerase (PARP) inhibitors. The recent discovery that some men with APC carry or develop alterations in DNA-damage repair proteins has uncovered a new therapeutic area. In May 2020, the FDA approved 2 oral PARP inhibitors, rucaparib (TRITON2) and olaparib (PROfound), for the treatment of mCRPC.[20,21] The TRITON2 study assessed objective response to rucaparib as compared to additional hormonal therapy for mCRPC patients with germline or somatic BRCA1 or BRCA2 mutations who had disease progression despite previously receiving at least 1 novel hormone therapy and 1 chemotherapy. The PROfound study was positive, showing a significant prolongation of radiographic progression-free survival but also OS in the patients with mCRPC after at least 1 novel androgen directed therapy (and up to 1 chemotherapy) who had BRCA1, BRCA2, and ATM mutations treated with olaparib as compared to an additional hormonal agent. Both agents, and others in study, will be trialed in combination and in earlier phases of the APC disease state.

Among mCRPC patients who have progressed through therapy and have poor performance status, these patients should be offered supportive care. The goal of palliation is to prevent and relieve suffering, and to support the best possible quality of life for the patient and family. Palliative radiotherapy can be an option to control bone pain in some patients and should be offered. Alternatively, in select cases clinicians may offer treatment with abiraterone + prednisone, enzalutamide, ketoconazole + steroid or radionuclide therapy. Currently, due to the poor performance status, clinicians should not offer systemic chemotherapy or immunotherapy to these patients.

The guidelines also address bone health and indicate that all patients with CRPC should be offered preventive treatment (supplemental calcium, vitamin D) to reduce the risk of fractures and skeletal related events.[22] Denosumab or zoledronic acid may be selected as preventive treatment for skeletal related events in patients with mCRPC and bone metastases.[23,24] The treatment of APC is undergoing an evolution with multiple new agents on the horizon, from immune modulators to vaccines to novel antiandrogens. The development of next generation imaging with PSMA PET, the assessment of germline and somatic genetic alterations and the ability to target therapies based on these precision-based strategies gives rise to great optimism as we look to the future in treating men. In addition, use of approved agents is being trialed in earlier stages of the disease state. This course delivers AUA Guideline

→ Continued on page 5

updates, keeping clinicians abreast of this rapidly changing landscape of APC. ■

1. Siegel RL, Miller KD and Fuchs HE et al: Cancer Statistics, 2021. CA Cancer J Clin 2021; **71:** 7.
2. 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:** 1502.
3. Petrylak DP, Tangen CM, Hussain MH et al: Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 2004; **351:** 1513.
4. Ryan CJ, Smith MR, de Bono JS et al: Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013; **368:** 138.
5. Kantoff PW, Higano CS, Shore ND et al: Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010; **363:** 411.
6. de Bono JS, Oudard S, Ozguroglu M et al: Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomized open-label trial. Lancet 2010; **376:** 1147.
7. Scher HI, Fizazi K, Saad F et al: Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012; **367:** 1187.
8. National Cancer Institute: FDA Approval for Radium 223 Dichloride. Available at https://www.cancer.gov/cancertopics/druginfo/fda-radium-223-dichloride.
9. Beer TM, Armstrong AJ, Rathkopf DE et al: Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014; **371:** 424.
10. Smith MR, Saad F, Chowdhury S et al: Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med 2018; **378**: 1408.
11. Hussain M, Fizazi K, Saad F et al: PROSPER: a phase 3, randomized, double-blind, placebo (PBO)-controlled study of enzalutamide (ENZA) in men with nonmetastatic castration-resistant prostate cancer (M0 CRPC). J Clin Oncol, suppl., 2018; **36**: abstract 3.
12. Fizazi K, Shore N, Tamella TL et al: Darolutamide in nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2019; **380**: 1235
13. Bischoff-Ferrari HA, Willett WC, Wong JB et al: Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA 2005; **293**: 2257.
14. Hussain M, Tangen CM, Berry DL et al: Intermittent androgen deprivation suppression for rising PSA level after radiotherapy. N Engl J Med 2012; **367**: 895.
15. U.S. Food and Drug Administration: FDA Approves first PSMA-Targeted PET Imaging Drug for Men with Prostate Cancer. Washington, DC: U.S. Food and Drug Administration 2020. Available at https://www.fda.gov/news-events/press-announcements/fda-approves-first-psma-targeted-pet-imaging-drug-men-prostate-cancer.
16. U.S. Food and Drug Administration: FDA Approves Second PSMA-Targeted PET Imaging Drug for Men with Prostate Cancer. Washington, DC: U.S. Food and Drug Administration 2021. Available at https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-second-psma-targeted-pet-imaging-drug-men-prostate-cancer.
17. Pritchard CC, Mateo JJ, Walsh N et al: Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 2016; **375:** 443.
18. Lowrance WT, Breau RH, Chou R et al: Advanced prostate cancer: AUA/ASTRO/SUO Guideline PART I. J Urol 2021; **205**: 14.
19. Lowrance WT, Breau RH, Chou R et al: Advanced prostate cancer: AUA/ASTRO/SUO Guideline PART II. J Urol 2021; **205**: 22.
20. 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**: 3763.
21. De Bono J, Mateo J, Fizazi K et al: Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med 2020; **382:** 2091.
22. Saad F, Bögemann M, Suzuki K et al: Treatment of nonmetastatic castration-resistant prostate cancer: focus on second-generation androgen receptor inhibitors. Prostate Cancer Prostatic Dis 2021; **24:** 323.
23. Saad F, Gleason DM, Murray R et al: Long-term efficacy of zoledronic acid for the prevention of -hormone-refractory prostate cancer. J Natl Cancer Inst 2004; **96**: 879.
24. 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 randomized, double-blind study. Lancet 2011; **377:** 813.

AUA2021 PLENARY

Highlights Summary of the State-of-the-Art Lecture on: Personalized Medicine in the Management of Prostate Cancer across the Patient Care Continuum

Jack R. Andrews, MD
Author

Brian F. Chapin, MD
Author

Learning Objective

At the conclusion of the activity, participants will be able to:

- *Discuss personalized care for prostate cancer therapy including prognostic versus predictive markers, potential predictive markers and prospective trials, as well as barriers.*

A personalized approach to prostate cancer therapy is on the horizon, and while much work is being done in this arena, there is still much to accomplish. As is known, prostate cancer is the most prevalent cancer among men and can

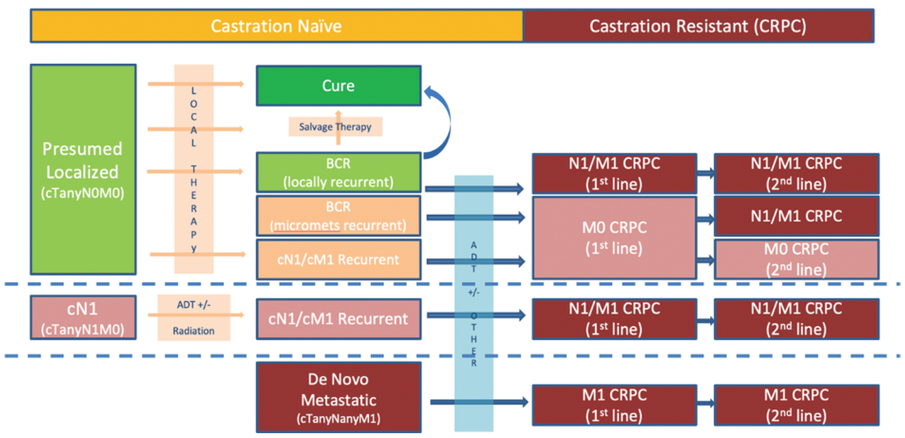


Figure 1. Various disease states in prostate cancer. *BCR*, biochemical recurrence. *CRPC*, castration resistant prostate cancer.

present in various disease states. Each stage of this disease (boxes in fig. 1) represents a timepoint with unique and varying prognostic variables. Through the years, we have further risk stratified (compartmentalized) patients with

→ Continued on page 6

prostate cancer by Gleason score, clinical and pathological stages, histology, and AUA/National Comprehensive Cancer Network® (NCCN®) risk categories, and more recently have begun to identify the varying biology.

As is known, not all patients with prostate cancer should be treated the same, and while risk stratification (NCCN, CAPRA etc) allows for improved prognostication, it has its limitations. Risk stratification also allows for improved balance in clinical trials and more accurate comparisons in retrospective studies with statistical balancing, such as matching or propensity score analysis. While compartmentalization/risk stratification can be helpful it can also generate bias. While a patient with Gleason score 10 prostate cancer and a patient with Gleason score 7 prostate cancer should obviously be managed differently, the prognosis and management can vary equally between 2 men with Gleason 7 prostate cancers with different underlying biology. Risk stratification is a helpful tool but alone is not granular enough to usher in the era of personalized medicine.

As personalization in prostate cancer becomes more and more prevalent, it is critically important to differentiate between prognostic biomarkers and predictive biomarkers. The terms are often used interchangeably, but they have very different meanings and implied consequences. The ability to interpret advances in personalization will require providers to recognize the difference between prognostic and predictive biomarkers and when/how to apply them in their practice.

A prognostic biomarker is a variable associated with favorable or unfavorable outcomes for patients in the absence of treatment. An example of a prognostic biomarker can be something as simple as prostate color (fig. 2). Over time, blue prostates have a more favorable survival than red prostates without or regardless of treatments applied. Therefore, prostate color is prognostic of survival outcome. Prostate color however cannot be used to determine whether a patient is more or less likely to respond to a specific treatment. Gleason score is an example of a real-world prognostic marker. Untreated Gleason score 7 prostate cancer will have less favorable outcomes compared to Gleason score 6 prostate cancer.

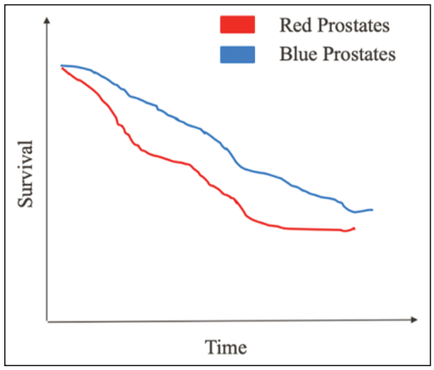


Figure 2. Example of prognostic biomarker.

A predictive biomarker is a variable used to identify or select for patients or groups of patients most likely to benefit from a specific therapy. A theoretical example would be prostates with high genetic risk have improved survival when Drug X is added to androgen deprivation therapy (ADT), while in prostates with low genetic risk no survival benefit is seen with the addition of Drug X to ADT (fig. 3). In this scenario, high genetic risk is a predictive biomarker for the addition of Drug X to ADT. An example of a real-world predictive biomarker in prostate cancer is DNA damage repair (DDR) mutations. Patients with DDR mutations have been shown to have improved survival with PARP inhibitor therapy compared to those patients without DDR mutations.[1] Therefore, a DDR mutation is predictive of a response to a PARP inhibitor but does not provide prognostic information in the absence of treatment.

Commonly, a prognostic biomarker will be used incorrectly to "predict" treatment response. For example, while genomic testing may provide additional prognostic information, it is important to know when to use a genomic test and how to interpret the results. Reflexive genomic testing is not recommended in all patients as it is often not helpful and sometimes even detrimental.[2,3] For example, genomic tests on prostate biopsy specimens are associated with pathological features on radical prostatectomy and may not be applicable to predicting eligibility for active surveillance.[4] When used incorrectly, genomic testing may be detrimental to patients by leading to overtreatment. Given the complexity of genomic screening indications, inappropriate reflexive genomic testing may further confuse patients and complicate treatment decisions unnecessarily. Additionally, to date no randomized trials in prostate cancer have demonstrated an improvement in patient outcomes based on genomic tests.

While it is important to utilize prognostic biomarkers and predictive biomarkers correctly, a biomarker can still be prognostic and predictive. In a 2017 *JAMA Oncology* manuscript by Zhao et al, the authors looked at 3,782 prostatectomy specimens and assessed PAM50 gene expression classifiers including Luminal A, Luminal B and Basal PAM50 expression.[5] The authors found that prostate cancer-specific mortality (PCSM) varies between the variable PAM50 expressions with Luminal A PAM50 expression having the longest PCMS and Basal PAM50 expression have the poorest PCSM. These data illustrate the prognostic role of PAM50 expression as a prognostic biomarker. The authors also evaluated the impact of ADT vs no ADT

→ Continued on page 7

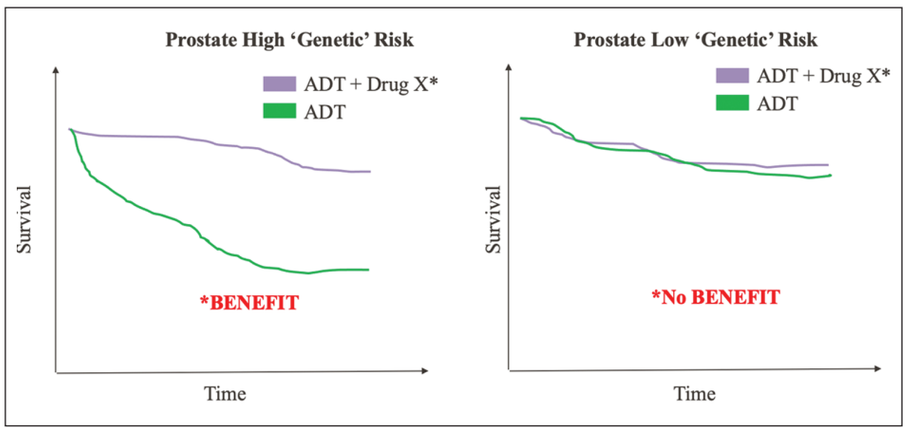


Figure 3. Example of predictive biomarker.

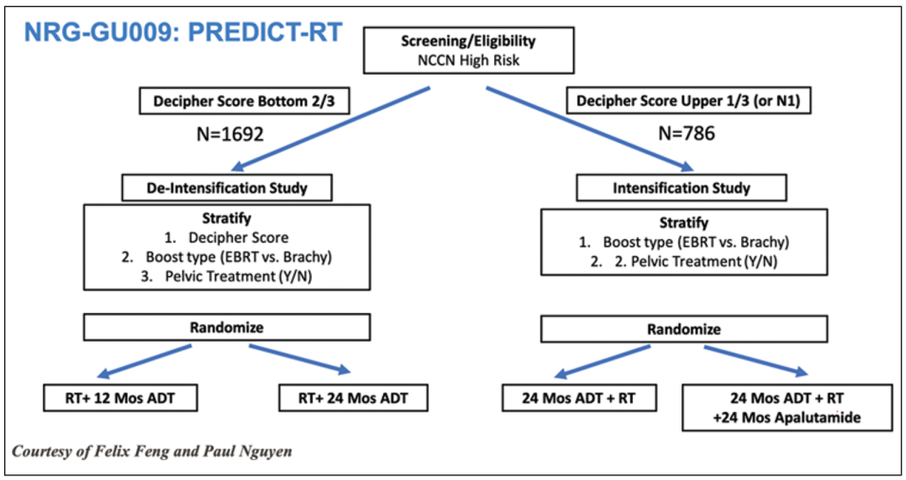


Figure 4. NRG-GU009 design schema (courtesy of Felix Feng and Paul Nguyen). *EBRT*, external beam radiation therapy. *Brachy*, brachytherapy.

in PAM50 gene expression. The results demonstrated that ADT provides a benefit in distant metastasis-free survival to patients with Luminal B PAM50 expression but not to those with Luminal A or Basal PAM50 expression. These data highlight the role of Luminal B PAM50 expression as a possible predictive biomarker for use of ADT to improve distant metastatic free survival.

Zhao et al also published a 2016 study looking at a 24 gene prediction score for postoperative radiation, called the Post-Operative Radiation Therapy Outcomes Score (PORTOS).[6] The 24 genes were selected from 196 men and were validated in a separate cohort of 330 men with clinical endpoints of metastasis free survival with a follow up time of 10 years. Men with a high PORTOS score had significantly improved distant metastasis-free survival when treated with radiation therapy (RT) compared to those with a low PORTOS score, in which there was no improvement with radiation. These results demonstrate the use of PORTOS as a potential predictive biomarker in the setting of postoperative radiation. An exciting potential area for investigation would be the use of PORTOS in the primary treatment of prostate cancer and if a high PORTOS in localized prostate cancer would predict improved benefit with primary radiotherapy. Future trials will hope to assess this and potentially validate in a prospective trial to inform if indeed these markers can be predictive.

Currently, NRG-GU009: PREDICT-RT Trial is an active trial prospectively evaluating the Decipher® Prostate RP Genomic Classifier for a potential role as a predictive biomarker. Decipher is a 22-gene classifier used to stratify risk of metastasis based on prostatectomy specimen analysis.[7] It is a prognostic biomarker and does not offer any validated prediction of treatment response. The trial design schema can be seen in figure 4 and shows the intensification/de-intensification trial design. Patients with a Decipher score in the bottom two-thirds will be de-intensified and randomized to RT+12 months of ADT or RT+24 months of ADT. Patients with a Decipher score in the top third will be intensified and randomized to RT+24 months of ADT or RT+24 months of ADT and apalutamide. This trial design is an exciting and interesting example of how to prospectively validate a potential predictive biomarker.

There are many exciting areas of development in personalized treatment of prostate cancer. While few predictive markers exist, it is realistic to think that many of the current prognostic markers could be validated as predictive markers using banked samples from prior prospective trials or with prospective evaluation. Another area of potential is to validate existing markers across earlier stages of the disease. Many markers, such as PAM50 and DDR mutations, are developed in the later stages of prostate cancer for many reasons. When markers are validated in earlier stages this clinical impact may be magnified. There are simply more patients in earlier stages of the disease and more expected longevity in which to realize the potential benefit of a personalized treatment. While personalized medicine is sure to change the management of prostate cancer, there are barriers to overcome prior to implementation. One barrier to consider when using biopsy samples is tumor heterogeneity. Prostate tumors are known to harbor multiple clonal populations and biomarker analysis based on a subdominant clone, which may mislead management. In addition to tumor heterogeneity, metastatic lesions are genetically dynamic as they respond to androgen receptor pathway drugs and chemotherapies. Because of this it may be necessary to reassess for predictive markers at multiple time points in the patient's care and likely will require multiple samples or evaluation of circulating tumor factors.

In conclusion, significant progress has been made in personalized care for the treatment of prostate cancer, but there is much work to be done. Practice-changing personalized medicine in prostate cancer is on the horizon, and clinicians will need to be prepared to interpret and implement biomarkers into practice. To assess biomarkers, it is critical to understand the differences between a prognostic biomarker and a predictive marker and how to assimilate that marker into practice. Validation of markers within prospective trials is needed, and skeptical optimism is appropriate until validations are complete. ■

1. de Bono J, Mateo J, Fizazi K et al: Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med 2020; **382:** 2091.
2. Eggener SE, Rumble RB, Armstrong AJ et al: Molecular biomarkers in localized prostate cancer: ASCO guideline. J Clin Oncol 2019; **38:** 1474.
3. Sanda MG, Cadeddu JA, Kirkby E et al: Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part I: risk stratification, shared decision making, and care options. J Urol 2018; **199:** 683.
4. Lin DW, Zheng Y, McKenney JK et al: 17-Gene genomic prostate score test results in the Canary Prostate Active Surveillance Study (PASS) cohort. J Clin Oncol 2020. **38:** 1549.
5. Zhao SG, Chang SL, Erho N et al: Associations of luminal and basal subtyping of prostate cancer with prognosis and response to androgen deprivation therapy. JAMA Oncol 2017; **3:** 1663.
6. Zhao SG, Chang SL, Spratt DE et al: Development and validation of a 24-gene predictor of response to postoperative radiotherapy in prostate cancer: a matched, retrospective analysis. Lancet Oncol 2016; **17:** 1612.
7. 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:** 374.

AUA2021 COURSE

Incorporating Genomic Testing for Prostate Cancer into Your Practice

Joseph R. Wagner, MD
Author, Course Director

Matthew R. Cooperberg, MD
Author, Faculty

Daniel W. Lin, MD
Author, Faculty

David F. Penson, MD
Author, Faculty

Learning Objectives

At the conclusion of the activity, participants will be able to:

- *Describe the seminal validation studies for prostate cancer genomic testing.*
- *List the different prognostic endpoints provided by various genomic tests.*
- *Identify appropriate genomic testing based on a patient's unique clinical characteristics.*
- *Review the AUA and National Comprehensive Cancer Network® guidelines for genomic testing for prostate cancer.*

Mounting evidence suggests genomic tests are useful through all stages of prostate cancer detection and treatment. "Incorporating Genomic Testing for Prostate Cancer into Your Practice" focuses on identifying a patient's unique clinical characteristics, assessing prognostic end points and reviewing AUA and National Comprehensive Cancer Network® guidelines for genomic testing for prostate cancer.

There are now multiple genomic tests for men at risk for, or diagnosed with, localized prostate cancer which can further risk assess the need for prostate biopsy, aid in making different treatment decisions (active surveillance, surgery, radiation etc), or impact the frequency of cancer monitoring. A patient might migrate away from a prostate biopsy to continued monitoring of his prostate specific antigen and be spared the diagnosis of a clinically insignificant prostate cancer or a complication with a negative biopsy. He may choose active surveillance over definitive therapy based on the result of genomic testing. 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 after primary therapy. 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 reviewed and underscore their importance in prostate cancer detection and treatment decision making. Although not all patients require genomic testing, they can be useful depending on the clinical circumstances.

Before discussing genomic testing, it is important to understand and agree on definitions. Germline tests examine mutations that are inherited from either parent and are present in each cell. Genomic tests examine somatic mutations in the tumor itself. As some tests lumped into this category are not examining mutations (ConfirmMDx®–hypermethylation, ExoDx™–extracellular vesicle RNA, various protein tests), they are sometimes referred to as molecular tests or assays. A brief biochemistry review showing the path from DNA to RNA to proteins illustrates tests utilize all of these molecules to provide the clinician with critical information.

> "Germline tests examine mutations that are inherited from either parent and are present in each cell. Genomic tests examine somatic mutations in the tumor itself."

In determining which patients to test, the first step for doctors should be to familiarize themselves with AUA and National Comprehensive Cancer Network guidelines as well as the genomic tests that are available. All the tests have different clinical end 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.

In the pre-diagnostic setting, our panel feels prostate specific antigen is an excellent biomarker for cancer but can be improved upon with adjunct tests. 4K, PHI, ExoDX, SelectMDx® and PCA3 can all be useful in deciding whether to proceed with a biopsy. These tests, along with ConfirmMDx, can also be helpful in deciding whether to proceed with a second biopsy. Add magnetic resonance imaging to the mix and it is clear the urologist has many tools at his disposal to aid in shared decision making.

Once diagnosed with clinically localized cancer, Prolaris®, Decipher®, OncotypeDX®, and ProMark® can all be used to help determine which patients are more appropriate for active surveillance or definitive therapy. Although all 4 tests have a common goal, all have different, though increasingly overlapping, clinical end points. Prolaris examines the 10-year prostate cancer specific mortality with watchful waiting and the 10-year risk of metastasis after definitive treatment. Decipher reports the 5 and 10-year risk of metastasis after definitive treatment, the 10-year risk of prostate cancer mortality after treatment, and the risk of adverse

→ Continued on page 9

"Prostate specific antigen is an excellent biomarker for cancer but can be improved upon with adjunct tests. 4K, PHI, ExoDX, SelectMDx® and PCA3 can all be useful in deciding whether to proceed with a biopsy."

pathology at surgery. Oncotype utilizes 10-year prostate cancer specific mortality, 10-year risk of metastasis, and adverse pathology, all after surgery. Finally, ProMark examines the risk of adverse pathology at surgery. In addition to categorizing men as appropriate for active surveillance versus treatment, recent studies have demonstrated Decipher can be used to identify patients more apt to benefit from concurrent androgen deprivation therapy with radiation.

In the post-prostatectomy setting, both Decipher (end point metastasis) and Prolaris (end point biochemical recurrence) can help identify men at higher risk for recurrence who may consider earlier adjuvant or salvage treatment. Once again, recent studies have demonstrated Decipher can be used to identify patients more apt to benefit from concurrent androgen deprivation therapy with radiation.

Men with high risk prostate cancer, a family history of germline mutations (BRCA, Lynch etc), Ashkenazi Jewish ancestry, a family history of prostate cancer–first degree (father/brother/son), or multiple Grade Group ≥2/<60 years or who died of prostate cancer, or ≥3 cancers on same side of family (colon, urothelial, breast, pancreas, ovarian)–should consider germline testing. If a germline mutation is discovered, they should be screened appropriately for other cancers for which they are at risk. Family members should be offered genetic counseling to discuss whether they would like to undergo testing. Finally, studies such as PROfound which showed radiographic progression-free survival for patients treated with PARP inhibitors with either *BRCA1, BRCA 2,* or *ATM* mutations demonstrate personalized medicine based on mutations is here today.

DNA, RNA and proteins are responsible for the current parameters (prostate specific antigen, Grade Group, etc) used to determine the clinical significance of prostate cancer. It is not surprising that these responsible molecules can be utilized themselves to provide information. Genomic tests are closely entwined with these traditional parameters, making them useful at all stages of prostate cancer treatment. The use of such tests is key for helping urologists stay current in a rapidly changing field. ■

"DNA, RNA and proteins are responsible for the current parameters (prostate specific antigen, Grade Group, etc) used to determine the clinical significance of prostate cancer. It is not surprising that these responsible molecules can be utilized themselves to provide information."

AUA2021 COURSE

Genetic Testing in Prostate Cancer: Understanding Clinical Implications for Early Detection, Localized Disease and CRPC

Todd M. Morgan, MD
Author, Course Director

Heather H. Cheng, MD, PhD
Faculty

Leonard G. Gomella, MD, PhD
Faculty

Learning Objectives

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 appropriate strategies for cancer screening.*
- *Identify the criteria for genetic testing of prostate cancer patients, the gene panels available and options for testing these men.*
- *Interpret results of genetic testing and relay this information to patients in order to facilitate shared decision making based on the test results.*
- *Utilize the results of genetic testing to improve outcomes among patients with metastatic prostate cancer, including recommendations regarding PARP-inhibition, chemotherapy and immunotherapy.*

→ Continued on page 10

Introduction

Over the past several years, our understanding of germline mutations as an important cause of aggressive prostate cancer has dramatically increased. 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 to optimize and refine the field of germline genetics in prostate cancer.

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).[1] For men who have first-degree relatives diagnosed with prostate cancer, the risk of developing the disease increases by roughly twofold compared to the general population. It is important to distinguish between hereditary prostate cancer (HPC) and familial prostate cancer. HPC is estimated to account for 5%-10% of prostate cancer cases. These are generally considered to be due to higher penetrance inherited genetic variants, such as mutations in *BRCA1* or *BRCA2*, and these variants can greatly increase lifetime risk. Familial prostate cancer is a broader term that encompasses 15%-20% of cases and can include those patients with a strong family history of prostate cancer but no detectable genetic mutations. More common polygenic variants with smaller effect sizes likely factor into many of these familial cases. These are often recognized as single nucleotide polymorphisms (SNPs), which may or may not themselves have a functional role in increasing the risk of developing prostate cancer.[2]

Germline Alterations

A number of genes 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 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.[3,4]

> "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."

Several options for germline genetic testing are now available for those men with prostate cancer who are at high risk of harboring a genetic alteration. 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 commercial 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 include genes without confirmed relevance to prostate cancer risk. Importantly, while insurance coverage continues to improve, not all carriers will cover germline testing even in those who meet guidelines-based criteria.

> "Men with *BRCA1/2* mutations have been shown in multiple studies to potentially have more aggressive prostate cancer and decreased survival compared to patients with sporadic prostate cancer."

Importantly, many variants identified on multi gene panel testing may not be clinically relevant. Some are known to be non-pathogenic, while others are indeterminate and classified as variants of uncertain significance (VUS). 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 VUS, or "gray area," result should be discussed with patients before any testing is performed.

Guideline Statements on Testing and Early Detection

In recognizing the importance of germline mutations, the National Comprehensive Cancer Network® (NCCN) Genetic/Familial High-Risk Assessment Guideline now distinguishes indications according to tumor characteristics vs. family/ancestry indications. Tumor-specific indications include: metastatic prostate cancer, high/very high risk prostate cancer, or intraductal/cribiform histology. Family history characteristics include 1 or more close blood relatives with: breast cancer diagnosed at ≤50 years of age; ovarian cancer; pancreatic cancer; or metastatic, intraductal/cribiform, or high/very high risk prostate cancer. Additional indications include 2 or more relatives with breast or prostate

→ Continued on page 11

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 exam in these high risk men. Furthermore, the guidelines suggest follow-up 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.[5,6] At the University of Michigan Prostate Cancer Risk Clinic, men who are known carriers of germline pathogenic mutations related to prostate cancer (e.g. *BRCA1*/2) are offered PSA screening and digital rectal exam 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.[7] This is combined with additional urine biomarker testing (SelectMDx) 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 (NCI) utilizes a similar algorithm but also adds multiparametric MRI (NCT03805919)

Treatment Implications

Men with *BRCA1/2* mutations have been shown in multiple studies to potentially have more aggressive prostate cancer and decreased survival 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 poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) 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 (mCRPC), having a DNA damage repair alteration appeared to predict response to olaparib.[8] 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.[9] Further evidence for the phase 3 PROFOUND trial demonstrated the efficacy of olaparib in mCRPC patients with a mutation in BRCA1, BRCA2, or ATM, leading to FDA approval in this setting.[10] 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 approval in BRCA1 and BRCA2 mutated mCRPC as well.[11]

> "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."

There is also evidence of increased sensitivity to platinum-based chemotherapy in metastatic prostate cancer patients with germline DNA repair mutations, likely related to platinum's mechanism of action through DNA damage.[12] 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 (www.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 mismatch repair (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.[13] The emerging data regarding MMR deficiency and checkpoint inhibition sensitivity have led to

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

→ Continued on page 12

an FDA approval for pembrolizumab, a PD-1 inhibitor, in solid tumors with mismatch repair deficiency such as in Lynch syndrome.[14] 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, 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:** 75.
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:** 419.
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:** 186.
4. Tryggvadottir L, Vidarsdottir L, Thorgeirsson T et al: Prostate cancer progression and survival in BRCA2 mutation carriers. J Nat Cancer Inst 2007; **99:** 929.
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:** 831.
6. Castro E, Mikropoulos C, Bancroft EK et al: The PROFILE feasibility study: targeted screening of men with a family history of prostate cancer. Oncol 2016; **21:** 716.
7. Sessine MS, Das S, Park B et al: Initial findings from a high genetic risk prostate cancer clinic. Urology 2021; doi: https://doi.org/10.1016/j.urology.2021.05.078.
8. Mateo J, Carreira S, Sandhu S et al: DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 2015; **373:** 1697.
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:** 443.
10. Hussain M, Mateo J, Fizazi K et al: Survival with olaparib in metastatic castration-resistant prostate cancer. N Engl J Med 2020; **383:** 2345.
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:** 3763.
12. Cheng HH, Pritchard CC, Boyd T et al: Biallelic inactivation of BRCA2 in platinum-sensitive metastatic castration-resistant prostate cancer. Eur Urol 2016; **69**: 992.
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:** 2460.
14. Boyiadzis MM, Kirkwood JM, Marshall JL et al: Significance and implications of FDA approval of pembrolizumab for biomarker-defined disease. J Immunothe Cancer 2018; **6:** 35.

AUA2021 COURSE

Common Dilemmas in Prostate Cancer Detection and Management

Gerald L. Andriole, Jr., MD
Author, Moderator/Course Director

Anthony V. D'Amico, MD, PhD
Author, Faculty

Adam S. Kibel, MD
Faculty

A. Oliver Sartor, MD
Faculty

Learning Objectives

At the conclusion of the activity, participants will be able to:

- *Optimally use prostate specific antigen (PSA) and other biomarkers to minimize unnecessary testing and biopsy when screening men who are at average risk for prostate cancer.*
- *Apply the principles of "risk-adapted" screening for men at elevated risk for prostate cancer based on race, family history, early in life PSA, polygenic risk scores and specific genetic mutations (eg BRCA1/2).*
- *Identify the roles of MRI, high frequency ultrasound and novel transperineal approaches to improve prostate biopsy.*
- *Treat men with locally advanced prostate cancer with multimodal approaches and how to choose and sequence hormonal, chemotherapeutic, immunologic and/or targeted approaches (eg PARP inhibitors) in men with metastatic and castrate resistant prostate cancer.*
- *Explain how to choose and sequence secondary and tertiary hormonal, chemotherapeutic, immunologic and/or targeted therapies (eg PARP inhibitors) in men with metastatic and castrate resistant prostate cancer.*

Our course reviewed prostate cancer screening with prostate specific antigen (PSA) and other biomarkers, techniques of biopsy and imaging of prostate cancer using magnetic resonance imaging (MRI), microultrasound and positron emission tomography (PET) scans, and treatment of advanced and recurrent prostate cancer.

There are multiple markers designed to improve our ability to identify men at high risk for prostate cancer who should be aggressively screened. Genetic testing looking at various single nucleotide polymorphisms (SNPs) (aka polygenomic risk score using, for example, PROMPT test) and/or looking for high-penetrance abnormalities in DNA repair genes (such as BRCA1 and 2)

→ Continued on page 13

can significantly assess an individual's risk for prostate cancer and guide when to start screening. Individuals with high polygenomic risk scores or defects in these genes should be screened starting at age 40 and annually.

New data support PSA screening annually in African American (AA) men. AA men are significantly less likely to present with M1 prostate cancer or die from prostate cancer with annual screening over a 5-year period as opposed to less frequent opportunistic PSA testing. While this was not randomized, it is important given that AA men are at high risk for developing more aggressive prostate cancer and were under-represented in the prospective PSA screening studies (PLCO and ERSPC).[1]

If any patient has an elevated PSA, multiple serum and urinary biomarkers are available to provide the patient with an individualized risk assessment for prostate cancer. These biomarkers by and large perform similarly to avoid 20%–40% of benign biopsies at a cost of missing a small proportion (usually less than 5%) of clinically significant cancers.

The urine tests are PCA3, ExoDx® and SelectMDx.[2,3] Each requires collection of first catch urine. In all cases, an elevated value is associated with increased risk. The utility of the test is primarily to avoid biopsy in men with a low value since they are less likely to have significant disease. Similarly, serum based tests such as PHI and 4KScore may be used to guide biopsy decisions. Their utility is particularly useful in conjunction with MRI.

Comparison among the available biomarkers is difficult as head-to-head studies are not presently available. For now practitioners should individually evaluate the properties of the available reflex biomarkers and choose the one that works best in their practice.

Prostate biopsy has changed dramatically because of the widespread recognition that conventional transrectal ultrasound (TRUS)-guided transrectal biopsy in the office often misses prostate cancer entirely and when it detects prostate cancer often under or overestimates tumor volume and/or Gleason score. Moreover, there is a concerning increase in infectious complications from transrectal biopsy. For these reasons, transperineal biopsy has had a resurgence. Contemporary approaches to transperineal biopsy can be performed under local anesthesia using the Precision Point or other transperineal access system. More comprehensive grid-guided template biopsies usually require sedation. Transperineal biopsy has a high detection rate as it enables assessment of all parts of the prostate. It has been studied in comparison to conventional biopsy for detection of cancer and for followup of patients on active surveillance; men having transperineal biopsy had a higher detection of significant cancer on initial biopsy and on followup biopsy (if on active surveillance) compared to those having conventional TRUS biopsy.[4]

Image-guided biopsy has been increasingly used. In comparison with conventional TRUS, MRI-targeted biopsy identifies more clinically significant cancer and a fewer insignificant cancers. The AUA, European Association of Urology and National Comprehensive Cancer Network recommend MRI imaging if available for biopsy naïve patients. Combined targeted and systematic cores are recommended; biopsy naïve patients with a normal MRI still require systematic biopsy. In patients with a prior negative biopsy, a negative MRI may avoid a repeat biopsy particularly if reflex biomarkers are favorable. Image-guided biopsy may also be performed using microultrasound, a 29 megahertz probe which results in a 300% improvement in resolution. It enables real-time targeting of suspicious regions of the prostate without image fusion and is completely under the control of the urologist. Microultrasound images of the prostate are categorized using the Prostrate Risk Identification using Micro Ultrasound (PRIMUS) system which is analogous to the Prostate Imaging–Reporting and Data System classification for MRI. The learning curve for microultrasound ranges between 15 and 40 cases. Microultrasound biopsies may be performed transrectally or transperineally and can also include fusion biopsies of MRI suspicious regions. Microultrasound yields similar sensitivity and negative predictive value to MRI in several single institution and 1 multi-institutional study.[5]

> "The AUA, European Association of Urology and National Comprehensive Cancer Network recommend MRI imaging if available for biopsy naïve patients."

New data show that docetaxel may significantly reduce and possibly eliminate radiation induced cancers which are often lethal. In a randomized study a subgroup of men with a PSA level <4 ng/ml were identified who had aggressive high-grade prostate cancer and whose survival seemed be prolonged when docetaxel was added to the standard treatment using radiation and hormonal therapy. This hypothesis is currently being tested using a meta-analysis of previously published randomized trials evaluating the impact of docetaxel when added to standard of care therapy (radical prostatectomy or radiation therapy [RT]/androgen deprivation therapy) on overall survival in men with high-risk prostate cancer.[6]

Three randomized trials published in September 2020 in *Lancet* and *Lancet Oncology* concluded that delivering RT after surgery for prostate cancer when the PSA rises signaling recurrence (ie early salvage RT) as opposed to when the PSA is undetectable (ie adjuvant RT) did not compromise subsequent cancer progression.

However, these trials may have missed the benefit of adjuvant RT due to lack of power because a minority of men (9%–17% of the study cohorts) were found to have adverse factors at prostatectomy which are associated with cancer progression and death from prostate cancer. Such men are those with high grade (Gleason score 8 to 10) prostate cancer that also extends outside the prostate (ie through the capsule, into the seminal vesicles, bladder neck or anterior rectal wall) or has spread into the pelvic lymph nodes.[7]

→ Continued on page 14

Moroever, men with adverse pathology at prostatectomy comprise the vast majority of men who go on to die from prostate cancer and therefore have the most to gain from adjuvant RT. Yet given the results of the 3 randomized trials, many physicians are no longer offering adjuvant RT, even in men with adverse pathology at surgery.

New data evidence to support that delivering adjuvant as compared to early salvage RT can reduce the risk of death by decreasing death from prostate cancer in men found to have adverse pathology at surgery.

These data should heighten awareness that men with adverse pathology at surgery may experience shortened survival due to an increase in death from prostate cancer if physicians wait for the PSA to rise to deliver RT (ie early salvage RT).

PET scanning has enhanced management of prostate cancer patients by more accurately staging intermediate and high risk patients and by allowing targeted salvage therapy in men with biochemical recurrence after primary treatment with surgery or radiation. Both prostate specific membrane antigen (PSMA) PET scans and fluciclovine PET scans are useful in the latter setting.[8,9]

The management of castrate resistant prostate cancer is becoming increasingly complex. A particularly notable change in recent years has been the introduction of novel hormonal agents into the castrate sensitive metastatic space as well as utilization of novel hormonal therapies for those with nonmetastatic castrate resistant disease. This changes the choices available for those now diagnosed with castrate resistant disease as well. Genetic alterations are important from several perspectives and a variety of guideline committees have suggested that all men with metastatic prostate cancer should have germline genetic testing.

With regard to castrate resistant metastatic prostate cancer in 2020 and 2021 there were 2 particularly notable developments. Poly ADP ribose polymerase (PARP) inhibitors were approved by the U.S. Food and Drug Association for those with selected homologous recombination repair defects, with patients harboring BRCA2 mutations having a high response rate in particular. Of note, patients with mismatch repair gene alterations (eg MSH2, MSH6) may respond robustly to PD1 inhibitors.[10] Importantly, there has been a rise in the importance of molecularly targeted radiation therapy, especially PSMA-targeted radioisotopes that now have been shown to prolong survival in advanced castrate resistant prostate cancer despite multiple prior therapies.[11] FDA approvals are anticipated for this innovative therapy in 2022. Other targeted therapies are in development. ■

1. Qiao EM, Kotha NV, Nalawade V et al: Association of increased intensity of prostate-specific antigen screening in younger African American men with improved prostate cancer outcomes. J Clin Oncol, suppl., 2021; **39:** 15.
2. Haese A, Trooskens G, Steyaert S et al: multicenter 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:** 256.
3. McKiernan J, Donovan M, Margolis E et al: A prospective adaptive utility trial to validate performance of a novel urine exosome gene expression assay to predict high-grade prostate cancer in patients with prostate-specific antigen 2–10 ng/ml at initial biopsy. Eur Urol 2018; **74:** 731.
4. Meyer A, Mamawada M, Winoker J et al: Transperineal prostate biopsy improves detection of clinically significant prostate cancer among men on active surveillance. J Urol 2021; **201:** 1069.
5. Klotz, L, Lughezzani, G, Maffei, D et al: Comparison of microultrasound and mpMRI for prostate cancer: A multicenter prospective analysis. Can Urol Assoc J 2021; **15:** E11.
6. D'Amico AV, Xie W, McMahon E et al: Radiation and androgen deprivation therapy with or without docetaxel in the management of nonmetastatic unfavorable-risk prostate cancer: a prospective randomized trial. J Clin Oncol 2021; **39:** 2938.
7. Tilki D, Chen MH, Wu J et al: Adjuvant versus early salvage radiation therapy for men at high risk for recurrence following radical prostatectomy for prostate cancer and the risk of death. J Clin Oncol 2021; **39:** 2284.
8. Hoffman MS, Lawrentschuk N, Francis R et al: PSMA PET CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy. Lancet 2020; **395:** 1208.
9. Andriole G, Kostakoglu L, Chau A et al: The impact of PET with 18-F Fluciclovine on the treatment of biochemical recurrence of prostate cancer: results from the LOCATE study. J Urol 2019; **201:** 322.
10. Hussain M, Mateo J, Fizazi K et al: Survival with olaparib in metastatic castration-resistant prostate cancer. N Engl J Med 2020; **383:** 2345.
11. Sartor O, de Bono J, Chi KN et al: Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. N Engl J Med 2021; **385:** 1091.

AUA2021 COURSE

What's New in the Management of Hormone Naïve and Castrate Resistant Prostate Cancer: A Case-Based Session for Urologists, Advanced Practice Providers and Teams

Judd W. Moul, MD, FACS
Author, Course Moderator/Director

Lawrence I. Karsh, MD, FACS
Faculty

Evan Y. Yu, MD
Faculty

Learning Objectives

At the conclusion of the activity, participants will be able to:

- *List the 3 main advanced prostate cancer disease states (HSMPC, M0 CRPC and M1 CRPC) and be able to identify these patients in urological practice.*
- *Identify FDA-approved hormonal and nonhormonal therapies for use in each of these 3 disease states: HSMPC, M0 CRPC, M1 CRPC.*
- *Demonstrate the safe use and unique mechanism of action and side effects of*

→ Continued on page 15

new and existing agents.
- *Explain the sequencing of novel therapies and be able to identify patient progression of disease by PSA, imaging, and signs and symptoms.*
- *Work in team care including urologists, advanced practice providers, oncology nursing, oncology pharmacy, medical oncology and radiation oncology and their support staffs.*

As the course director, I have been fortunate to host a course on advanced prostate cancer at the annual AUA since 2012, and the changes over these 10 years have been nothing less than breathtaking![1] Furthermore, this may have been the most "interesting" year with regard to the COVID-19 pandemic. We were all excited to meet live in Vegas, but this did not work out and we did our course virtually. The content is available on demand from the AUA until the end of 2021 at www.aua2021.org.

In the early years, 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 (M0) CRPC due to emerging data on use of apalutamide and enzalutamide in these men. 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, in 2020 and 2021, we are 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 year to consider based on this molecular testing.

Newly Diagnosed HS M1 Prostate Cancer

Five 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.[2,3] 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 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.[4]

In 2017 the LATITUDE trial showed that abiraterone added to ADT for men with new M1 disease resulted in a similar survival benefit as docetaxel.[5] In 2019, we learned that both apalutamide and enzalutamide also significantly extend survival compared to traditional ADT alone.[6–8] The results of TITAN (apalutamide) and ENZAMET and ARCHES (NCT02677896) (enzalutamide) were published showing robust benefits. In my mind, this is "Combined Androgen Blockade" or "Maximal Androgen Blockade" finally showing a survival benefit now using 2nd/3rd generation nonsteroidal antiandrogens.[9]

In TITAN, 1,052 men were randomized to traditional ADT alone vs ADT plus apalutamide (240 mg by mouth, daily).[6] 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.[10] 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.[7,8] 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) versus placebo (576). Recently, at ESMO 2021, my Duke Cancer Institute partner, Dr. Andrew Armstrong, presented the latest trial update. As of the data cut-off 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; $p < 0.0001$).

As noted earlier, these are the first trials to definitively prove the benefit of "Combined" or "Maximal" Androgen Blockade as first proposed by Labrie et al in the mid 1980s! Finally, the third generation nonsteroidal antiandrogens (being apalutamide and enzalutamide) prove beyond a reasonable doubt this long postulated concept.[10]

However, it is unclear if patients should receive docetaxel plus one of the oral agents or only 1 new therapy along with traditional ADT. The above noted ENZAMET trial did not confirm a survival benefit (at 3 years) to adding enzalutamide to men who received early docetaxel. Furthermore, no head-to-head comparisons allow us to determine which oral agent among the 3 is "better." However, the key message for urologists is that traditional ADT alone for their patients with newly diagnosed M1 HS prostate cancer is not the current standard of care for the majority of men.[11,12]

CRPC

Since 2010, multiple new agents have been approved by the FDA for M1 CRPC, including sipuleucel-T,

→ Continued on page 16

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.[13–16]

Bone Health/Denosumab

Denosumab is prescribed at a dose of 120 mg (trade name XGEVA®) subcutaneously monthly to prevent skeletal related events in men with M1 CRPC with bone metastases.[17] The FDA also approved a 60 mg dose (trade name Prolia®) subcutaneously twice a year to prevent bone loss (osteopenia and osteoporosis) in men without bone metastases who are on gonadotropin-releasing hormone (GnRH) 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 asymptomatic or minimally symptomatic M1 CRPC.[18] The ideal patient for sipuleucel-T should have documented clinical metastases and a rising prostate specific antigen while on continuous hormonal therapy. The patient should not have bone or cancer pain requiring narcotic pain medications. In men with prostate specific antigen levels in the lowest quartile of the IMPACT trial (prostate specific antigen 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.[19] At the virtual course in 2021, we also discussed the data from the PROSEED registry (1,902 patients) treated with sipuleucel-T in real-world practice between 2011–2014. In a retrospective analysis of 219 African-American men disease-matched to a Caucasian cohort, OS was 35.3 months vs 25.8 months.[20] These intriguing data need to be confirmed in prospective fashion.

Abiraterone

Abiraterone is a 17-lyase and 17-hydrolase inhibitor that blocks key pathways in the steroidal synthesis pathways leading to androgen production.[21] 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 FDA-approved for use in men with newly diagnosed HS M1 prostate cancer in February 2018.[22] Approval was based on LATITUDE (NCT01715285), a placebo controlled international clinical trial that randomized 1,199 patients with metastatic high risk disease. Patients received 1,000 mg abiraterone acetate orally once daily with 5 mg prednisone once daily (in 597) or matching placebos orally once daily (in 602). Patients in both arms received a GnRH analogue or underwent bilateral orchiectomy. The major efficacy end point was OS. Median OS was not estimable and 34.7 months in the abiraterone acetate and placebos 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 next generation androgen receptor antagonist, was FDA-approved in 2012 to treat men with disease that progressed after docetaxel based chemotherapy based on level 1 evidence from the AFFIRM trial.[23] It received an expanded approved 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 unlike abiraterone it does not require prednisone. However, enzalutamide does have an approximately 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 3, randomized, double-blind, placebo controlled study of enzalutamide in men with M0 CRPC.[24] It demonstrated an approximately 2-year metastasis-free survival benefit over placebo showing that metastasis-free survival 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.[25]

In the setting of M1 hormone-sensitive 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.[26] The data from the SPARTAN trial showed that apalutamide delayed metastasis-free survival 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

→ Continued on page 17

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 "combined androgen blockade" ending a 30+-year quest 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.[27] 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 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.[28] 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.[29]

Darolutamide

In mid 2019, darolutamide was FDA-approved for M0 CRPC based on the ARAMIS trial making this the 3rd agent approved (apalutamide, enzalutamide and darolutamide) in this disease state.[30] This 3rd generation nonsteroidal oral antiandrogen prolonged metastases-free survival also by approximately 2 years compared to placebo in M0 CRPC and more recently showed an OS advantage.[31] 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 hormone-sensitive prostate cancer with the ARASENS trial. This interesting trial design compares ADT plus darolutamide plus 6 cycles of docetaxel vs ADT plus docetaxel plus placebo.

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 CHEK. 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).[13–16]

Rucaparib is a PARP inhibitor that is approved for patients with BRCA alterations; however, the label is only in the post-docetaxel setting. Olaparib offers a survival benefit (from the PROFOUND trial) for this patient population, and does not mandate prior receipt of docetaxel chemotherapy. Pembrolizumab is tissue/site agnostic for microsatellite instability high and hypermutated solid tumors.[13-16]

Summary

The management of advanced prostate cancer continues to evolve in exciting and sometimes unexpected ways, and 2021 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' actionable germline or somatic mutations. ■

1. Komura K, Sweeney CJ, Inamoto T et al: Current treatment strategies for advanced prostate cancer. Int J Urol 2018; **25:** 220.
2. Sweeney CJ, Chen YH, Carducci M et al: Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015; **373:** 737.
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:** 1163.
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:** 1080.
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:** 338.
6. Chi KN, Agarwal N, Bjartell A et al: Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med 2019; **381:** 13.
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:** 121
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:** 2974.
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:** 956.

→ Continued on page 18

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:** 2294.
11. Lowrance WT, Breau RH, Chou R et al: Advanced prostate cancer: AUA/ASTRO/SUO guideline PART I. J Urol 2021; **205:** 14.
12. Lowrance WT, Breau RH, Chou R et al: Advanced prostate cancer: AUA/ASTRO/SUO guideline PART II. J Urol 2021; **205:** 22.
13. Siebert AL, Szymaniak BM, Numan Y et al: Genetically informed prostate cancer treatment for metastatic disease. Urol Clin North Am 2021; **48:** 365.
14. LeVee 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.
15. 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:** 3763.
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:** 395.
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:** 813.
18. Handy CE and Antonarakis ES: Sipuleucel-T for the treatment of prostate cancer: novel insights and future directions. Future Oncol 2018; **14:** 907.
19. Schellhammer PF, Chodak G, Whitmore JB et al: 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; **81:** 1297.
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:** 4172.
21. Caffo O, Veccia A, Kinspergher S et al: Abiraterone acetate and its use in the treatment of metastatic prostate cancer: a review. Future Oncol 2018; **14:** 431.
22. Fizazi K, Tran N, Fein L et al: Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 2017; **377:** 352.
23. Scott LJ: Enzalutamide: A review in castration-resistant prostate cancer. Drugs 2018; **78:** 1913.
24. Hussain M, Fizazi K, Saad F et al: Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2018; **378:** 2465.
25. Sternberg CN, Fizazi K, Saad F et al: Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2020; **382:** 2197.
26. Smith MR, Saad F, Chowdhury S et al: Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med 2018; **378:** 1408.
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:** 1028.
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:** 213.
29. Mizokami A, Kimura G, Fujii Y et al: 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:** 1629.
30. Fizazi K, Shore N, Tammela TL et al: Darolutamide in nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2019; **380:** 1235.
31. Fizazi K, Shore N, Tammela TL et al: Nonmetastatic, castration-resistant prostate cancer and survival with darolutamide. N Engl J Med 2020; **383:** 1040.

AUA2021 COURSE

Advanced Prostate Cancer

Rachel Hastings, MS, PA-C
Author

Anne Calvaresi, DNP, CRNP, RNFA
Course Director

Jim Kovarik, MS, PA-C
Course Director

Learning Objective

At the conclusion of the activity, participants will be able to:

- *Assess current approaches and explore new strategies for clinical management of advanced prostate cancer.*

The management of advanced prostate cancer (APC) has undergone some major changes in recent years from patient evaluation to treatment secondary to the addition of many new treatments to our toolbox by way of recent genetics and clinical trials. Although only 6% of our prostate cancer patients will initially present with distant disease, we know that the implications on quality of life and prognosis are great.

PSA/ Doubling time:	*Pathology:*	*Radiographic findings:*	*Genetic testing:*
Disease Stage		*Treatment Options**	
Rising PSA with no radiographic evidence of metastatic disease		☐ Observation ☐ Clinical trial enrollment ☐ Hormone therapy	
Metastatic hormone-sensitive disease		☐ Hormone therapy ☐ Androgen-synthesis inhibitor ☐ Second-generation anti-androgen (androgen receptor inhibitor) ☐ Chemotherapy ☐ Radiotherapy	
Nonmetastatic castration-resistant disease		☐ Hormone therapy ☐ Second-generation anti-androgen ☐ Observation	
Metastatic castration-resistant disease		☐ Hormone therapy ☐ Androgen-synthesis inhibitor	
Nonmetastatic castration-resistant disease		☐ Hormone therapy ☐ Second-generation anti-androgen ☐ Observation	
Metastatic castration-resistant disease		☐ Hormone therapy ☐ Androgen-synthesis inhibitor ☐ Second-generation anti-androgen ☐ Chemotherapy ☐ Immunotherapy ☐ Radiopharmaceutical ☐ PARP inhibitor	

**Only select therapies may be recommended within each treatment class for specific disease stages. Clinicians should refer to full clinical guidelines for specific recommendations.*

Figure. Treatment checklist.[15]

Evaluation

A thorough patient evaluation can have impacts on screening, treatment choice and initiation of lifestyle modification. We need to consider ethnicity, family history of cancer or genetic mutations, body mass index, tobacco use, diet and biopsy/imaging findings.

Recent advances in genetics highlight the importance of proper patient evaluation and screening. This will continue to evolve as guidelines and clinical pathways catch up with the data. Finding out about germline mutations or somatic mutations is crucial for our high-risk patients because these patients can now benefit from more targeted treatments as well as provide risk assessment for family members (germline).

Germline testing is easily sampled (swab or tissue) and is recommended for high-risk or metastatic disease, but also patients with lower risk but with strong family history or adverse pathological features such as intraductal/cribriform cell types. Somatic mutation testing is performed with tissue biopsy and can help with treatment decision making. All in all, 20% will have additional treatment options as a result of testing; 10% will have inherited or germline mutations with BRCA2 being the most common, ~20%–25% will have homologous recombination deficiencies and will benefit from PARP inhibitors, and 5%–7% of patients will have mismatch repair deficiencies/microsatellite disabilities and will benefit from our immune checkpoint inhibitors.[1–3]

Imaging evaluation is newly expanding as well. Currently our definitions of metastatic disease use traditional imaging modalities, but as magnetic resonance imaging and prostate specific membrane antigen positron emission tomography become more readily available and help us to better characterize the extent of disease after biochemical recurrence these guidelines will potentially shift and may result in reclassification of patients beyond M0.[4]

Treatment

For over 60 years our treatment option for our patients with APC was androgen deprivation therapy (ADT) and ADT alone, and in the last 15 years genetics and clinical trials have directly resulted in several lines of Food and Drug Administration approved systemic therapies that are indicated for various disease states (see figure).

> "Screening and early diagnosis are paramount as they can lead to individualized treatment strategies for patients with APC."

Disease States

Biochemical Recurrence: Biochemical recurrence is defined as a detectable prostate specific antigen (PSA) that rises on 2 consecutive measurements or does not fall to undetectable levels. Unfortunately, about 20%–30% of our patients treated with intent to cure will fall into this category. Our treatment options for these patients start with observation alone and continue with conventional as well as newer options. This decision is based on risk derived from age and comorbidities, pathological features, time to PSA recurrence and PSA velocity. As more men are afforded the opportunity for treatment long before they develop distant metastasis, we must weigh long-term survival vs treatment effects/quality of life issues as we trend toward younger, healthier men in this category.

It is well-known that ADT has many long-term considerations and/or complications and we must especially as Advanced Practice Providers remain diligent when it comes to monitoring by way of blood work, bone density, cardiac monitoring and adherence to appointments; prevention/mediation by way of encouraging/facilitating smoking cessation, decreased alcohol consumption, vitamin supplementation, heart healthy diet, brain training and maybe most importantly a continuous exercise regimen. Patient support services/survivorship programs are crucial for these patients.

Metastatic Hormone Sensitive Prostate Cancer: These patients can be asymptomatic or minimally symptomatic. Our treatments here include ADT alone or with the addition of a next generation oral anti-androgen (abiraterone, enzalutamide, apalutamide, darolutamide) or systemic chemotherapeutic agents (docetaxel). Data from the LATITUDE, STAMPEDE and ARCHES trials have made combination therapy standard of care for these patients. Our choices are determined by prognostic indicators as well as side effect profiles. ADT alone is still appropriate for patients with poor cardiac function or significant comorbidities. Abiraterone must be given with prednisone because of increased mineralocorticoid activity. Prednisone is not necessary with enzalutamide, apalutamide or darolutamide but these agents carry the risk of seizures and multiple drug interactions. We consider addition of chemotherapy in the patient with high-volume (visceral metastasis and/or at least 4 bone lesions, including at least 1 distant bony lesion) hormone sensitive metastatic prostate cancer.[5–8]

Nonmetastatic Castration Resistant Prostate Cancer: Nonmetastatic castration resistant prostate cancer is defined as PSA progression without evidence of metastatic disease in patients receiving hormonal therapy with castrate levels of testosterone. This definition currently utilizes conventional imaging and not new modalities such as prostate specific membrane antigen positron emission tomography. This subset of patients may be largely impacted in the coming years as our imaging improves.

The SPARTAN, PROSPER and ARAMIS studies found that treatment with ADT plus abiraterone, enzalutamide or darolutamide increased the time to metastasis, and the earlier you add these medications to ADT the longer men live, no matter what treatment they get later.[9–11] Chemotherapy and immunotherapy currently do not have a role in the management of patients with nonmetastatic castration resistant prostate cancer.

Metastatic Castration Resistant Prostate Cancer: Metastatic castration resistant prostate cancer is defined as PSA progression with the development of new metastasis despite castration levels (T<50) of testosterone. Our treatment toolbox for these patients has many additions over the last few years. We now have the above treatments as well

→ Continued on page 20

as immunotherapy, radium and targeted therapies. When talking about this subset of patients and deciding on treatment we want to apply 3 questions: Are they symptomatic? Have they received chemotherapy? And What is their performance status? The paradigms are shifting in terms of when to add to ADT and focus on timing and layering or sequencing of these newer agents with targeted treatments. We know that chemotherapy works best for patients with high-volume disease. Sipuleucel T is our immunotherapeutic option. The ideal patient for sipuleucel T is asymptomatic or minimally symptomatic with no liver metastasis. It is of note with this medication to counsel patients as we often do not see a decline in PSA or improvement in scans despite survival benefit. All metastatic castration resistant prostate cancer patients should receive genetic testing to determine if they will benefit from PARP inhibitors. These are for patients with homologous recombination genes such as BRCA, ATM and CHEK2. Olaparib is offered to patients with a somatic or germline DNA repair gene mutation after treatment with an oral androgen receptor targeted agent.[12] Rucaparib is offered to patients with a germline or somatic BRCA1 or BRCA2 after treatment with an oral androgen receptor targeted agent and taxane-based chemotherapy.[13] Radium-223 is used to target bone lesions and only used if no visceral metastasis. Of note, this should not be used with abiraterone secondary to increased risk of fracture. Checkpoint immunotherapy (pembrolizumab/nivolumab) is one of our newer options for targeted treatment for patients with deficient DNA mismatch repair genes.[14]

AUA Index Patients

Asymptomatic, Good Performance Status: These patients have a rising PSA, documented metastasis on imaging, no prior chemotherapy and are asymptomatic, not requiring pain medication. Here we will offer a next generation oral hormone, chemotherapy or sipuleucel T. This is the ideal patient for this immunotherapeutic agent.

Symptomatic, Good Performance Status: Patients are included in this category if they have a rising PSA and documented metastasis on imaging but also have symptoms attributable to their cancer. Treatment options here include docetaxel, abiraterone and enzalutamide, as well as radium if pain secondary to disease burden. Patient selection is important here as chemotherapy shows maximal benefit in patients with high volume disease.

Symptomatic, Poor Performance Status: Treatment options are abiraterone, enzalutamide, docetaxel and radium-223 if performance status parallels disease.

Much of these guidelines are extrapolated or based on expert advice secondary to trial limitations but it is important to consider treatment for these patients especially if their poor performance status is attributable to their disease or disease burden. This is also important as we are seeing younger patients in this category secondary to younger patient trends.

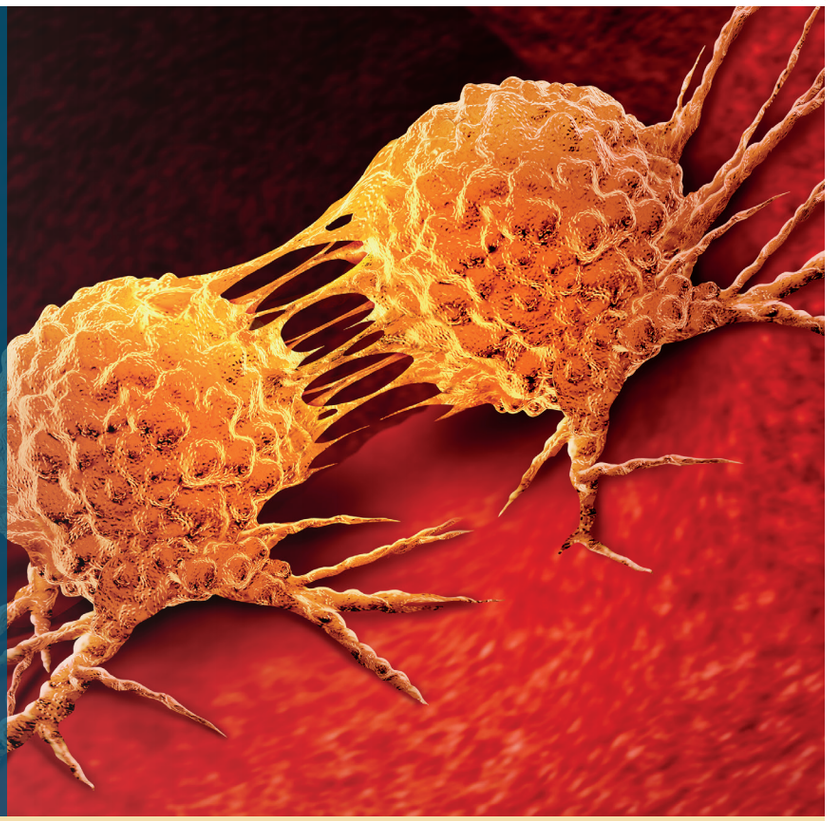
Symptomatic, Good Performance, Prior Docetaxel: As patients are now receiving earlier ADT and subsequently earlier becoming castration resistant and thereby offered docetaxel there remains a subset of patients who still have good performance status and can be offered immunotherapy. These patients will benefit most from layering with abiraterone, cabazitaxel, enzalutamide, docetaxel and radium.

Symptomatic, Poor Performance, Prior Docetaxel: Care should be focused on palliation for these patients but select patients can benefit from next generation oral hormones or targeted radionucleide.

Over the last decade, we have seen considerable advances in the biological understanding of APC resulting in the development of novel agents and treatment paradigms. Unfortunately, despite these significant strides APC remains a fatal disease, highlighting the need to continue to improve the care of these patients. Screening and early diagnosis are paramount as they can lead to individualized treatment strategies for patients with APC.

Optimized treatment of men with APC requires a multidisciplinary team to follow side effects, enroll in trials, ensure adherence to appointments, and maintain overall physical and mental health. As Advanced Practice Providers, we are frequently the cornerstone of this treatment team. Through shared decision making and patient education, we can make a meaningful impact on these patients' overall health and maximize their quality of life. ■

1. Giri VN, Knudsen KE, Kelly WK et al: Role of genetic testing for inherited prostate cancer risk: Philadelphia Prostate Cancer Consensus Conference 2017. J Clin Oncol 2018; **36:** 414.
2. Nicolosi P, Ledet E, Yang S et al: Prevalence of germline variants in prostate cancer and implications for current genetic testing guidelines. JAMA Oncol 2019; **5:** 523
3. Prichard CC, Mateo J, Walsh MF et al: Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 2016; **375:** 443.
4. Maurer T, Eiber M, Schwaiger M et al: Current use of PSMA-PET in prostate cancer management. Nat Rev Urol 2016; **13:** 226.
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 randomised controlled trial. Lancet 2016; **387:** 1163.
6. Fizazi K, Tran N, Fein LE et al: LATITUDE: A phase III, double-blind, randomized trial of androgen deprivation therapy with abiraterone acetate plus prednisone or placebos in newly diagnosed high-risk metastatic hormone-naive prostate cancer. J Clin Oncol, suppl., 2017; **35:** abstract LBA3.
7. Armstrong AJ, Szmulewitz RZ, Petrylak DP et al: Phase III study of androgen deprivation therapy (ADT) with enzalutamide (ENZA) or placebo (PBO) in metastatic hormone-sensitive prostate cancer (mHSPC): the ARCHES trial. J Clin Oncol, suppl., 2019; **37:** abstract 687.
8. Sweeney CJ, Chen YH, Carducci M et al: Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015; **373:** 737.
9. Smith MR, Saad F, Chowdhury S et al: Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med 2018; **378:** 1408.
10. Sternberg CN, Fizazi K, Saad F et al: Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2020; **382:** 2197.
11. Fizazi K, Shore N, Tammela TL et al: Nonmetastatic, castration-resistant prostate cancer and survival with darolutamide. N Engl J Med 2020; **383:** 1040.
12. de Bono J, Mateo J, Fizazi K et al: Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med 2020; **382:** 2091.
13. Abida W, Campbell D, Patnaik A et al: Non-BRCA DNA damage repair gene alterations and response to the PARP inhibitor rucaparib in metastatic castration-resistant prostate cancer: analysis from the phase II TRITON2 study. Clin Cancer Res 2020; **26:** 2487.
14. De Bono JS, Goh JCH, Ojamaaet K et al: KEYNOTE-199: Pembrolizumab (pembro) for docetaxel-refractory metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol, suppl., 2018; **36:** abstract 5007.
15. American Urological Association and Pfizer Oncology: Steps to Success: Improving Advanced Prostate Cancer Patient Management and Care Coordination. American Urological Association 2021. Available at https://www.auanet.org/documents/practices-resources/quality/quality-improvement-library/Steps%20to%20Success%20Improving%20Advanced%20PCa%20Patient%20Management%20and%20Care%20Coordination.pdf.



The AUA Expert Exchange Podcast:

Discussions in GU Cancer

Stream 8 interactive interview style episodes on the management of GU cancer. Episodes will cover topics across Prostate Cancer, Urothelial Carcinoma, and Kidney Cancer.

This series has been designed to improve urologist's ability to care for patients with prostate cancer, urothelial carcinoma, and advanced kidney cancers. The eight interview-style episodes will increase the clinician's competence in the application of new and emerging treatment options.

Subscribe to the AUA*University* podcast to access weekly episodes.

Available on Apple Podcasts and Google Play Music.

ACKNOWLEDGEMENTS:
This educational series is supported by independent educational grants from Astellas, AstraZeneca, Lantheus Medical Imaging, Merck and Pfizer, Inc.

ACCREDITATION:
The American Urological Association (AUA) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

CREDIT DESIGNATION:
The American Urological Association designates this enduring material for a maximum of 4.00 *AMA PRA Category 1 Credit™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

American Urological Association

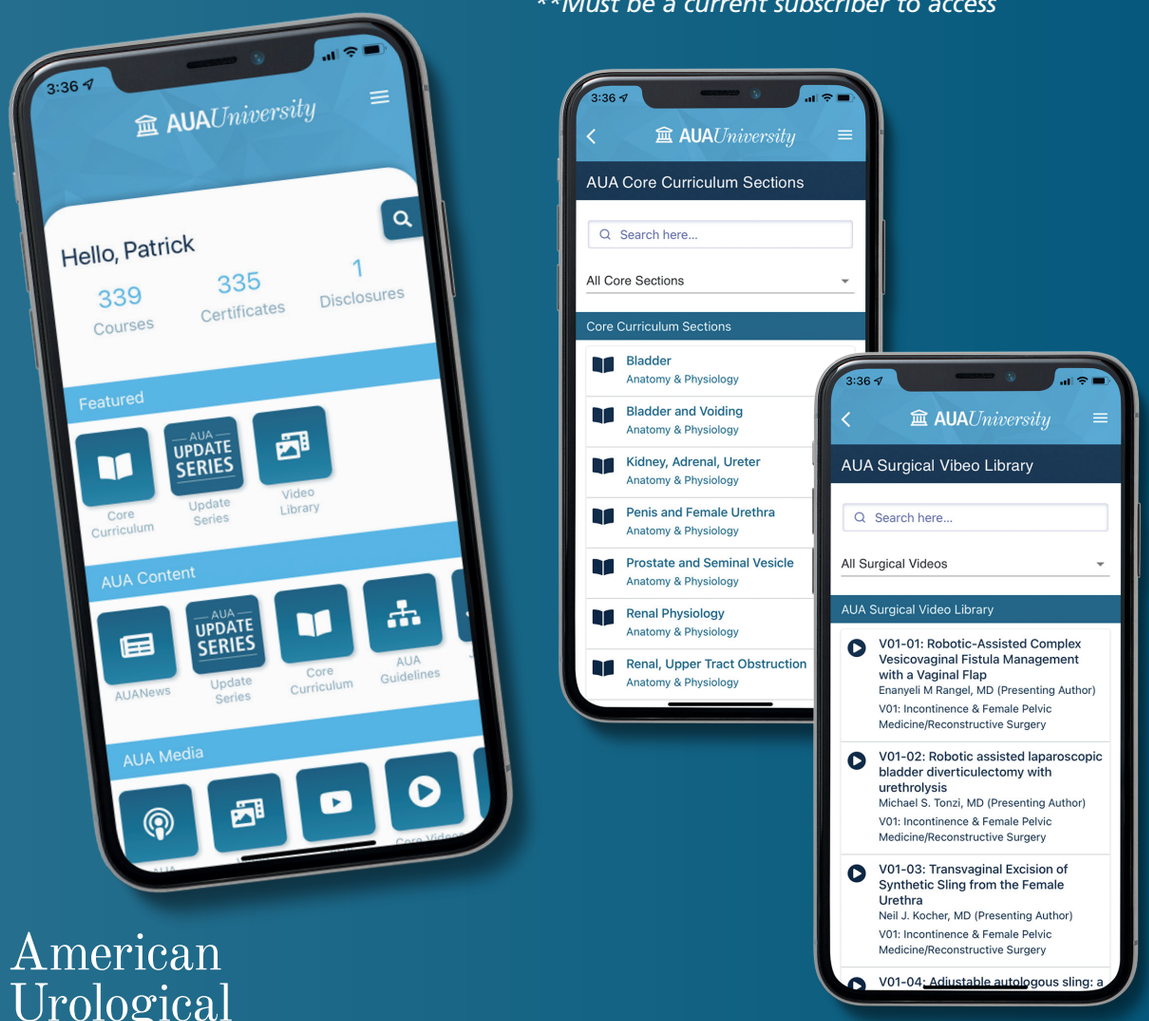
Listen Now!

AUA*University App*

The AUA*University* app provides instant access to search across AUA's popular clinical content.

- Urology Core Curriculum*
- AUA Update Series**
- Surgical Video Library*
- AUA Guidelines
- AUA*University* Podcasts
- AUA*University* YouTube
- *AUA News*

**AUA Member Benefit*
***Must be a current subscriber to access*



American Urological Association

LIVE *from* AUA 2021

American Urological Association

AUA2022 New Orleans

MAY 13-16

SAVE THE DATE

REGISTRATION OPENS IN DECEMBER!

AUANET.ORG/2022