Reaching for Health Equity in Prostate Cancer Care Through Advocacy

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**INDICATION**
LYNPARZA is a poly(ADP-ribose) polymerase (PARP) inhibitor indicated in combination with abiraterone and prednisone or prednisolone (abi/pred) for the treatment of adult patients with deleterious or suspected deleterious BRCA-mutated (BRCAm) metastatic castration-resistant prostate cancer (mCRPC). Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.

**PROpel: A phase 3 trial**
PROpel examined the efficacy of LYNPARZA + abi/pred vs placebo + abi/pred (active comparator) upon mCRPC diagnosis

- **Population** (N=796): mCRPC with or without HRR mutations
- **Patients** were randomized 1:1 to receive either LYNPARZA (300 mg QD) + abiraterone (1000 mg QD) with prednisone or prednisolone (5 mg BID) (n=399) or placebo + abiraterone (1000 mg QD) with prednisone or prednisolone (5 mg BID) (n=400). LYNPARZA was continued until objective radiological disease progression determined by investigator or unacceptable toxicity. All patients received a GnRH analog or had prior bilateral orchiectomy
- **Patients** were stratified by metastatic site and whether they received prior docetaxel at mHSPC stage. BRCAm status was not a stratification factor. Prior abiraterone was not allowed

**Trial endpoints:**
- **Primary endpoint (ITT):** rPFS by investigator assessment
- **Additional efficacy outcome measure (ITT):** Overall survival
- **Safety and tolerability**
- **Exploratory BRCAm subgroup analyses**
  - Investigator-assessed rPFS and OS in patients with BRCAm mCRPC (n=85)
  - Sensitivity analysis of rPFS by BICR

BRCAm status was assessed after randomization and before primary analysis by both NGS-based tumor tissue and ctDNA tests. BRCAm classification criteria in line with the FDA-approved assays were used to determine the deleterious and suspected deleterious somatic or germline mutation status of patients.

**IMPORTANT SAFETY INFORMATION**
**CONTRAINDICATIONS**
There are no contraindications for LYNPARZA.

**WARNINGS AND PRECAUTIONS**
Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML):
Occurred in approximately 1.5% of patients exposed to LYNPARZA monotherapy, and the majority of events had a fatal outcome. The median duration of therapy in patients who developed MDS/AML was 2 years (range: ≤6 months to >10 years). All of these patients had previous chemotherapy with platinum agents and/or other DNA-damaging agents, including radiotherapy.

Do not start LYNPARZA until patients have recovered from hematological toxicity caused by previous chemotherapy (≥ Grade 1). Monitor complete blood count for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities, interrupt LYNPARZA and monitor blood count weekly until recovery.

If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. Discontinue LYNPARZA if MDS/AML is confirmed.

**Pneumonitis:** Occurred in 0.8% of patients exposed to LYNPARZA monotherapy, and some cases were fatal. If patients present with new or worsening respiratory symptoms such as dyspnea, cough, and fever, or a radiological abnormality occurs, interrupt LYNPARZA treatment and initiate prompt investigation. Discontinue LYNPARZA if pneumonitis is confirmed and treat patient appropriately.

**Venous Thromboembolism (VTE):** Including severe or fatal pulmonary embolism (PE) occurred in patients treated with LYNPARZA. In the combined data of two randomized, placebo-controlled clinical studies (PROfound and PROpel) in patients with metastatic castration-resistant prostate cancer (N=1180), VTE occurred in 8% of patients who received LYNPARZA, including pulmonary embolism in 6%. In the control arms, VTE occurred in 2.5%, including pulmonary embolism in 1.5%. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism, and treat as medically appropriate, which may include long-term anticoagulation as clinically indicated.

**Embryo-Fetal Toxicity:** Based on its mechanism of action and findings in animals, LYNPARZA can cause fetal harm. Verify pregnancy status in females of reproductive potential prior to initiating treatment.

**Females**
Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months following the last dose.

**Males**
Advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of LYNPARZA and to not donate sperm during this time.

**ADVERSE REACTIONS**—Metastatic Castration-Resistant Prostate Cancer in Combination with Abiraterone and Prednisone or Prednisolone
Most common adverse reactions (Grades 1-4) in ≥10% of patients who received LYNPARZA/abiraterone with a difference of ≥5% compared to placebo for PROpel were: anemia (48%), fatigue (including asthenia) (38%), nausea (30%), diarrhea (19%), decreased appetite (16%), lymphopenia (14%), dizziness (14%), and abdominal pain (13%).

Most common laboratory abnormalities (Grades 1-4) in ≥20% of patients who received LYNPARZA/abiraterone for PROpel were: decrease in hemoglobin (97%), decrease in lymphocytes (70%), decrease in platelets (23%), and decrease in absolute neutrophil count (23%).
FDA approval of LYNPARZA + abi/pred was based on an exploratory BRCAm subgroup

LYNPARZA + abi/pred demonstrated improvement in rPFS vs placebo + abi/pred in patients with BRCAm mCRPC1,5

**BRCAm subgroup (n=85)**
- rPFS events, n (%): 14/47 (30) with LYNPARZA + abi/pred and 28/38 (74) with placebo + abi/pred
- Results from the BICr assessment were consistent with the investigator-assessed rPFS results

OS analysis: 70% reduction in risk of death (HR=0.30 [95% CI: 0.15–0.59]) for LYNPARZA + abi/pred vs placebo + abi/pred. OS events, n (%): 13/47 (28) and 25/38 (66), respectively

BRCAm status was not a stratification factor in PROpel, and analysis was not controlled for Type 1 error

**ITT population (n=796)**
Statistically significant improvement in rPFS was observed for LYNPARZA + abi/pred compared with placebo + abi/pred. OS for LYNPARZA + abi/pred compared to placebo + abi/pred did not reach statistical significance in the ITT population

**Patients without an identified BRCAm (n=711)**
Results from exploratory analyses in this subgroup (rPFS; HR=0.77 [95% CI: 0.63–0.96] and OS; HR=0.92 [95% CI: 0.74–1.14]) indicated that the improvement in the ITT population was primarily attributed to the results seen in the BRCAm subgroup

**IMPORTANT SAFETY INFORMATION (Cont’d)**

**DRUG INTERACTIONS**
- **Anticancer Agents**: Clinical studies of LYNPARZA with other myelosuppressive anticancer agents, including DNA-damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.
- **CYP3A Inhibitors**: Avoid coadministration of strong or moderate CYP3A inhibitors when using LYNPARZA. If a strong or moderate CYP3A inhibitor must be coadministered, reduce the dose of LYNPARZA. Advise patients to avoid grapefruit, grapefruit juice, Seville oranges, and Seville orange juice during LYNPARZA treatment.
- **CYP3A Inducers**: Avoid coadministration of strong or moderate CYP3A inducers when using LYNPARZA.

**USE IN SPECIFIC POPULATIONS**
- **Lactation**: No data are available regarding the presence of olaparib in human milk, its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in the breastfed infant, advise a lactating woman not to breastfeed during treatment with LYNPARZA and for 1 month after receiving the final dose.
- **Pediatric Use**: The safety and efficacy of LYNPARZA have not been established in pediatric patients.
- **Hepatic Impairment**: No adjustment to the starting dose is required in patients with mild or moderate hepatic impairment (Child-Pugh classification A and B). There are no data in patients with severe hepatic impairment (Child-Pugh classification C).
- **Renal Impairment**: No dosage modification is recommended in patients with mild renal impairment (CCr ≥ 50 mL/min estimated by Cockcroft-Gault). In patients with moderate renal impairment (CCr 31–50 mL/min), reduce the dose of LYNPARZA to 200 mg twice daily. There are no data in patients with severe renal impairment or end-stage renal disease (CCr ≤ 30 mL/min).

Please see accompanying Brief Summary of Prescribing Information on the following pages.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.


abi/pred=abiraterone plus prednisone or prednisolone; BICr=blinded independent central review; BID=twice daily; BRCAm=BRCA-mutated or BRCA mutation; CCI=confidence interval; ctDNA=circulating tumor DNA; GnRH=gonadotropin-releasing hormone; HR=hazard ratio; HRR=homologous recombination repair; ITT=intent-to-treat; mCRPC=metastatic castration-resistant prostate cancer; nHSPC metastatic hormone-sensitive prostate cancer; NGS=next-generation sequencing; NR=not reached; OS=overall survival; PARPi=poly (ADP-ribose) polymerase inhibitor; PCWG3=Prostate Cancer Working Group 3; QD=once daily; RECIST=Response Evaluation Criteria in Solid Tumors; rPFS=radiological progression-free survival.

Choose LYNPARZA + abi/pred as initial therapy for BRCAm mCRPC to help give your patients more time without disease progression.

![Freeze icon]

LYNPARZAhrpchp.com to explore additional data from the PROpel trial

LYNPARZA is a registered trademark of the AstraZeneca group of companies. ©2023 AstraZeneca. All rights reserved. US-75382 6/23
BRCA-mutated Metastatic Castration-Resistant Prostate Cancer in combination with Abiraterone and Prednisone or Prednisolone

- Patients with mCRPC should also receive a granulocyte-macrophage colony-stimulating factor (GM-CSF) such as lenograstim or should have had leukotriene.

Dosage Modifications for Adverse Reactions
- Manage adverse reactions, consider interruption of treatment or dose reduction. The recommended dose reduction is 250 mg taken twice daily.

Dosage Modifications for Concomitant Use with Strong or Moderate CYP3A Inhibitors
- Avoid concomitant use of strong or moderate CYP3A inhibitors with Lynparza.
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Dose reduction of Lynparza due to adverse reactions occurred in 21% of patients treated in the Lynparza with abiraterone arm. The most common (>2%) adverse reactions requiring dosage reductions of Lynparza were anemia (11%) and fatigue (7.5%).

The most common adverse reactions (>10%) in patients who received Lynparza/abiraterone were anemia (48%), fatigue (38%), nausea (30%), diarrhea (19%), decreased appetite (16%), lymphopenia (14%), abdominal pain (13%), and diastolic (14%).

Tables 18 and 19 summarize adverse reactions and laboratory abnormalities in PROpel, respectively.

### Table 18 Adverse Reactions (≥10%) in Patients Who Received Lynparza (with a Difference of ≥5% Compared to Placebo) in PROpel

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Lynparza/abiraterone n=396</th>
<th>Placebo/abiraterone n=396</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grades 1-4 (%)</td>
<td>Grades 3-4 (%)</td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td>Decrease in hemoglobin</td>
<td>97 12 81 1.3</td>
<td></td>
</tr>
<tr>
<td>Decrease in lymphocytes</td>
<td>70 23 49 11</td>
<td></td>
</tr>
<tr>
<td>Decrease in platelets</td>
<td>70 12 40 0.3</td>
<td></td>
</tr>
<tr>
<td>Decrease in absolute neutrophil count</td>
<td>23 5 6 0</td>
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<td>Grades 3-4 (%)</td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td>Anemia*</td>
<td>48 16 18 3.3</td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>14 5 6 1.8</td>
<td></td>
</tr>
<tr>
<td>Fatigue (including asthenia)</td>
<td>38 2.3 30 1.5</td>
<td></td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>30 0.3 14 0.3</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19 1 10 0.3</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13 0 7 0.5</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15 1 7 0</td>
<td></td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic*</td>
<td>14 0.3 7 0</td>
<td></td>
</tr>
</tbody>
</table>

### Table 19 Selected Laboratory Abnormalities Reported in ≥20% of Patients in PROpel

<table>
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Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Lynparza. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

### Immune System Disorders

Hypersensitivity including angioedema.

### Adverse Reactions

The most common adverse reactions (≥10%) in patients who received Lynparza plus abiraterone were headache (9%), VTE (8%), rash (7%), dysgeusia (6%), acute kidney injury (3%), and stomatitis (2.5%).

### Pediatric Use

Safety and effectiveness of Lynparza have not been established in pediatric patients.

### Geriatric Use

Safety and effectiveness of Lynparza have not been established in patients aged ≥65 years, and this included 95 (24%) patients who were aged ≥75 years.

### Safety and effectiveness of Lynparza were observed between these patients and younger patients.

### Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action (see Clinical Pharmacology (12.1) in the full Prescribing Information), Lynparza can cause fetal harm when administered to a pregnant woman. There are no available data on Lynparza use in pregnant women to inform the drug-associated risk. In an animal reproduction study, the administration of olaparib to pregnant rats during the period of organogenesis caused teratogenicity and embryo-fetal toxicity at exposures below those in patients receiving the recommended human dose of 300 mg twice daily (see Data). Apprise pregnant women of the potential hazard to the fetus and the potential risk for loss of the pregnancy.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. The estimated background risk in the U.S. general population of major birth defects is 2-4%, and the risk of spontaneous abortion is approximately 15-20% in clinically recognized pregnancies.

### Drug Interactions

Use with Anticancer Agents

Clinical studies of Lynparza with other myelosuppressive anticancer agents, including DNA damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.

### Effect of Other Drugs on Lynparza

Co-administration of CYP3A inhibitors can increase olaparib concentrations, which may increase the risk for adverse reactions (see Clinical Pharmacology (12.3) in the full Prescribing Information). Avoid co-administration of strong or moderate CYP3A inhibitors. The strong or moderate inhibitor must be co-administered, the dose of Lynparza to [see Dosage and Administration (2.4) in the full Prescribing Information].

Strong and Moderate CYP3A Inhibitors

Concomitant use with a strong or moderate CYP3A inducer decreased olaparib exposure, which may reduce Lynparza efficacy (see Clinical Pharmacology (12.3) in the full Prescribing Information). Avoid co-administration of strong or moderate CYP3A inducers.

### USE IN SPECIFIC POPULATIONS

#### Pregnancy

Risk Summary

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### Data

Animal Data

In a fertility and early embryonic development study in female rats, olaparib was administered orally for 14 days before mating through to Day 6 of pregnancy, which resulted in increased post-implantation loss at a dose level of 15 mg/kg/day (with maternal systemic exposures approximately 7% of the human exposure (AUC[0-24h]) at the recommended dose).

In an embryo-fetal development study, pregnant rats received oral doses of 0.05 and 0.5 mg/kg/day olaparib during the period of organogenesis. A dose of 0.5 mg/kg/day (with maternal systemic exposures approximately 0.18% of human exposure (AUC[0-24h]) at the recommended dose) caused embryo-fetal toxicities including increased post-implantation loss and major malformations of the eyes (anophthalmia, microphthalmia), vertebrae/ribs (extra ribs or ossification center, fused or absent neural arches, ribs, and sternum), skin (fused ectodermis), and diaphragm (hermia). Additional abnormalities or variants included incomplete or absent ossification (vertebra/sternum, ribs, limbs) and other findings in the vertebrae/sternum, pelvic girdle, lung, thymus, liver, urogenital, and umbilical artery. Some findings noted above in the eyes, ribs, and uterus were observed at a dose of 0.35 mg/kg/day olaparib at lower incidence.

#### Lactation

Risk Summary

No data are available regarding the presence of olaparib in human milk, or on its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in the breastfed infants from Lynparza, advise a lactating woman not to breastfeed during treatment with Lynparza and for one month following the last dose.

### Females and Males of Reproductive Potential

Lynparza can cause fetal harm when administered to a pregnant woman (see Use in Specific Populations (8.1) in the full Prescribing Information).

#### Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating treatment with Lynparza.

### Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with Lynparza and for 6 months following the last dose.

Males

Based on findings in genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of Lynparza. Advise male patients not to donate sperm during therapy and for 3 months following the last dose of Lynparza (see Use in Specific Populations (8.1) and Nonclinical Toxicology (13.1) in the full Prescribing Information).

### Pediatric Use

Safety and effectiveness of Lynparza have not been established in pediatric patients.

### Geriatric Use

Safety and effectiveness of Lynparza have not been established in patients aged ≥65 years, and this included 95 (24%) patients who were aged ≥75 years.

### Safety and effectiveness of Lynparza were observed between these patients and younger patients.

### Renal Impairment

No dosage modification is recommended in patients with mild renal impairment (CLcr 30 to 60 mL/min estimated by Cockcroft-Gault). Reduce Lynparza dosage to 200 mg twice daily in patients with moderate renal impairment (CLcr 15 to 30 mL/min) estimated by Cockcroft-Gault). Reduce Lynparza dosage to 200 mg twice daily in patients with severe renal impairment or end-stage disease (CLcr < 30 mL/min) (see Clinical Pharmacology (12.3) in the full Prescribing Information).

### Hepatic Impairment

No adjustment to the starting dose is required in patients with mild or moderate hepatic impairment (Child-Pugh classification A and B). There are no data in patients with severe hepatic impairment (Child-Pugh classification C) (see Clinical Pharmacology (12.3) in the full Prescribing Information).

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LYNPARZA® (olaparib) tablets, for oral use
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AUANews

September 2023, Volume 28 | Issue 9

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Reaching for Health Equity in Prostate Cancer Care Through Advocacy

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Prostatic cancer remains a prevalent condition with broad impact in US men. The American Cancer Society estimates that in 2022 there were approximately 268,490 new cases of prostate cancer and approximately 34,500 deaths caused by prostate cancer in the United States. Globally, a total of 1,414,259 new cases of prostate cancer and 375,304 related deaths were reported in 2020. However, the burden of this disease is not shared equally across the population. Health inequities in prostate cancer care have been well established along the entire continuum of this disease: from screening and early detection to treatment outcomes and cancer survivorship.1,2

The drivers of racial and socioeconomic health disparities in prostate cancer screening, diagnosis, treatments, and outcomes are multifactorial and complex and have been expertly summarized in several recent articles, such as Lillard et al.3 Understanding and reducing these disparities require an integrated approach, from clinical care to public policy. One of the strategies to attain health equity in prostate cancer care is through legislative and regulatory advocacy. This is where the missions of the AUA Diversity, Equity and Inclusion (DE&I) Committee and the AUA Public Policy Council overlap and have recently sparked impactful collaboration (Figures 1 and 2).

One example is the AUA Annual Urology Advocacy Summit, which affords urologists a unique opportunity to visit Capitol Hill lawmakers and advocate for meaningful changes. Our advocacy efforts in support of the Veterans’ Prostate Cancer Treatment and Research Act illustrate merits of these efforts. This legislation supports a comprehensive standardized system of treatment for veterans as well as a real-time registry and research to track patients’ progress. Clinical pathways are critical for establishing better health outcomes for veterans and are based on multidisciplinary research. A prostate cancer clinical pathway would cover a patient’s prostate cancer journey from early detection to advanced disease and end-of-life care.4

The AUA has championed this legislation since 2019 and included it in the legislative priorities during the 2019 AUA Summit during our Capitol Hill meetings (Figure 3). The bill unanimously passed the House of Representatives on September 22, 2020. Because legislation often requires multiple sessions of Congress to become law, we

Figure 1. Dr Larissa Bresler, AUA Diversity, Equity and Inclusion (DE&I) Committee Chair and Chief Diversity Officer of the AUA North Central Section.

Figure 2. AUA Diversity, Equity, and Inclusion Committee.

Figure 3. Welcome back to Capitol Hill! Pictured left to right: Norm Smith, MD; Representative Rodney Davis (D-IL 07); Peter Bajic, MD; Larissa Bresler, MD.

“Understanding and reducing these disparities require an integrated approach, from clinical care to public policy. One of the strategies to attain health equity in prostate cancer care is through legislative and regulatory advocacy.”

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Gregory Broderick Southeastern
Pamela Coleman Mid-Atlantic
Gabriela Gonzalez Western
Tomas Grebling SouthCentral
Nathan Grunewald North Central

Continued on page 8
continued our legislative advocacy in the following Congress. The bill was reintroduced in the House and Senate in 2021 and was eventually passed into law as part of the year-end Consolidated Appropriations Act in 2022. Implementation of this advocacy success story will begin this year.

The recent 2023 AUA Advocacy Summit also featured collaboration of the Public Policy Council and DE&I Committee. Denise Asafu-Adjei, MD, MPH, who is the AUA DE&I Committee Pipeline Workgroup leader and the 2023 AUA Gallagher Scholar, provided an overview of this year’s main legislative priorities and congressional “asks” during the first day of the Summit. Several advocacy initiatives facilitated reaching for health equity in prostate cancer care. A number of other DE&I Committee members, including the Chief Diversity Officer, also attended the Summit and contributed to the AUA advocacy efforts.

A focus of the 2023 Summit was the PSA Screening for Him Act. AUA joined with ZERO–The End of Prostate Cancer, along with more than 20 patient advocacy organizations and other stakeholders from across the prostate cancer community, to support this new bill co-sponsored by members in both the Senate and the House. In 2023, the incidence of prostate cancer was expected to increase for the first time in 20 years, likely because of changes to the screening guidelines over the last decade. African American men have a disproportionately higher rate of prostate cancer and are 70% more likely to be diagnosed with prostate cancer than White men. Moreover, African American men are 2.3 times more likely to die from prostate cancer, and are diagnosed with more aggressive disease and at younger ages compared to White men in settings of equal access to treatment. This racial disparity in mortality is currently the most pronounced among all cancers in the United States. Reducing health disparities in prostate cancer will require lowering barriers for screening to maximize the early detection of cancer when it is at its most treatable and least lethal stage. The bill waives deductibles, copayments, and coinsurance for prostate cancer screenings for those at highest risk of developing the disease, such as men with a family history of prostate cancer or those who are African American. This important bill aims to decrease the financial toxicity of screening and improves access to early detection.

Achieving health equity in prostate cancer care requires concerted and collaborative efforts by patient advocacy groups, stakeholder organizations, and professional groups like the AUA, including the Public Policy Council and DE&I Committee.


PROSTATE CANCER

Novel Molecular Profiling Technology Applications: Finding the Needle in a Haystack

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The recent advent of spatial transcriptomic technologies and single-cell sequencing has the potential to revolutionize our understanding of complex diseases with unprecedented insights into the molecular and cellular heterogeneity of tissues. Traditional bulk RNA sequencing has been instrumental in identifying key genes and pathways associated with different disease states; however, this approach averages gene expression signals across all cells within a tissue sample, masking the underlying cellular heterogeneity and cell-to-cell interactions. Spatial transcriptomics, highlighted as Nature Methods 2021 technology of the year, allows for the investigation of gene expression patterns within intact tissue sections while maintaining spatial context. By characterizing the spatial distribution of diseased or tumor cells, immune and stromal cells, as well as other components, researchers can unravel the intricate interactions and communication networks within a tissue. Spatial resolution is particularly important in the study of heterogeneous and complex diseases like prostate cancer. In this article, we describe the applications of spatial transcriptomics and single-cell sequencing in urological research with special emphasis on prostate cancer.

One spatial transcriptomic platform is digital spatial profiling (DSP) by NanoString Technologies. It utilizes a combination of spatially barcoded oligonucleotides and digital counting to quantify RNA molecules in regions of interest (ROIs). The tissue sample is sectioned onto a slide and ROIs are identified based on their spatial location, relevant histology, and/or morphology markers (see Figure). Barcoded oligonucleotide probes called GeoMx DSP spatial capture agents are hybridized to the tissue to capture and amplify RNA transcripts within the ROI. The captured RNA is then detected using fluorescently labeled reporter probes and imaged using a fluorescence microscope. This digital counting approach allows for precise quantification of gene expression levels in each region (see part B of Figure). To understand the molecular differences between peripheral zone (PZ) and
tumor may be needed to truly understand and potentially overcome the issue imposed by heterogeneity. The above spatial transcriptomic platforms provide spatially resolved information for very small areas or regions ranging from a few to hundreds of cells. Until very recently, the lack of single-cell or subcellular resolution has been a limitation for certain applications in spatial technology. In parallel to the development of spatial platforms, single-cell sequencing has emerged as a powerful technique to analyze individual cells within a sample, providing detailed insights into cellular diversity and heterogeneity. By profiling the transcriptome of individual cells, researchers can identify rare cell populations, characterize cell states, and uncover cell-to-cell variability. Single-cell sequencing can be performed using several technologies, such as droplet-based methods like Dropseq or Chromium Systems by 10x Genomics, or plate-based methods like Smart-seq. Applying single-cell sequencing to prostate cancer research has enabled the identification and characterization of rare cell populations, such as cancer stem cells or therapy-resistant cells, which play crucial roles in tumor initiation, progression, and treatment resistance. By dissecting the molecular features of these cells, researchers can develop targeted therapies to eliminate or inhibit their growth, thereby improving treatment outcomes. Moreover, single-cell sequencing has provided insights into the heterogeneity of cancer-associated immune cells within prostate tumors. Immune cell populations, such as T cells, macrophages, and dendritic cells, can exhibit diverse functional states and phenotypes within the tumor microenvironment. Understanding this complexity is crucial for...

Figure. A, Hematoxylin and eosin (H&E) image of radical prostatectomy specimen displaying prostate cancer in the peripheral zone. B, Immunofluorescence (IF) image using morphology markers to delineate the nucleus (SYTO13—blue), epithelium (PanCK—green), stroma/smooth muscle (SMA/ACTA2—yellow), and immune cell (CD45—red) components of the tumor. The H&E and IF images are then combined to select regions of interest (ROIs; 7 ROIs in this case) and segment ROIs into areas of interest (AOIs; 12 AOIs in this case) for digital spatial profiling using the NanoString Technologies platform.

Another spatial platform is Visium Spatial Gene Expression by 10x Genomics. This platform uses demarked regions on a slide with thousands of spots per region where each spot contains millions of mRNA capture probes with a barcode unique to that spot. The tissue specimen is laid over the slide and solubilized so that the overlying mRNA is captured in each spot and then sequenced. Our group utilized Visium to elucidate the transcriptomic changes that occur in the prostate over time after orchietomy in association with changes in the tissue architecture. We orchiec-tomized mice and then performed Visium spatial transcriptomics on the prostate at days 10, 15, and 20 in comparison to the sham. We also obtained single cell RNAseq from the prostates of 2 additional mice at days 0 and 15 post-orchiectomy to provide true single-cell resolution and found good concordance between the single-cell and Visium spatial findings, which allowed mapping of the single-cell data onto the spatial transcriptomic data. We found notable changes in androgen response genes that varied between prostate lobes as well as drastic changes in immune cell regulation and cell motility. Characterization of each cell in a...
developing immunotherapies and optimizing treatment strategies.7

The field of molecular profiling technology and techniques continues to evolve rapidly. New technologies incorporating both single-cell and spatial resolution have begun to emerge. One such platform is the NanoString CosMx spatial molecular imager, which uses in situ hybridization of barcoded mRNA probes with multiple rounds of reporter probe hybridization to produce subcellular level transcript localization. The platform, however, currently has a limitation of a 1,000-plex gene panel, though this is expected to increase over time. Our group utilized CosMx to explore the sarcomatoid transformation in renal cell carcinoma, which is thought to occur through an epithelial-to-mesenchymal transition. Both the single-cell and spatial resolution were crucial to our ability to detect a novel cell state along the epithelial-to-mesenchymal transition continuum as well as key interactions between the transitioning cells, macrophages, and CD8 T-cells. We believe this will lead to new biomarkers for immunotherapy response and potentially new therapeutic targets in kidney cancer. Critically, this integrative approach holds great promise for identifying novel biomarkers and therapeutic targets in prostate cancer.

Spatial transcriptomics and single-cell sequencing have already begun to revolutionize our understanding of malignancies including prostate cancer. These cutting-edge technologies provide insights into distinct cell populations, rare cell types, and cellular interactions in the tumor microenvironment. Such approaches open new avenues for discovery in the field and hold great promise for improving diagnosis, prognosis, and treatment strategies, leading to more personalized and effective therapies that target the dominant clones in cancer, the needle in a haystack. Moreover, advancements in spatial proteomic platforms and 3D multi-omics techniques are continuously evolving, offering exciting new possibilities. However, it is essential to carefully consider the necessity and suitability of these expensive technologies for addressing specific research inquiries as well as thoughtful integration into clinical care paradigms. With deliberate application, spatial biology has the potential to transform translational medicine, and we have only begun to scratch the surface of its capabilities.

PROSTATE CANCER

Peritoneal Interposition Flaps Subsequent to Robot-assisted Radical Prostatectomy: Impact on Lymphocele Incidences

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Radical prostatectomy is the standard surgical treatment for localized prostate cancer and is actually largely performed robotically in Western countries with appropriate economic structure.1 Bilateral pelvic lymphadenectomy (PLND) is recommended concomitantly for patients with intermediate- and high-risk prostate cancer.2,3 Although PLND allows invasive tumor staging, the curative potential of PLND remains unclear and is a major cause of peri- and postoperative complications.4 For symptomatic lymphoceles (sLC) as a direct consequence of PLND, rates between 2% and 10% have been reported in the literature.5 In this context, symptomatic means lymphoceles causing superinfection, lymphedema, lymphorrhea, hydronephrosis, pain, and compression of the internal iliac vein with consecutive deep vein thrombosis. Lymphoceles in general can be detected by computed tomography in almost every second patient. Men with high BMI and intraoperatively demanding conditions leading to prolonged surgery time are at risk for the postoperative occurrence of lymphoceles.6

Different surgical and nonsurgical strategies have been tried to reduce the rates of sLC after robot-assisted radical prostatectomy (RARP) and PLND. In this context, Lebeis et al published a pioneering study of a surgical modification which includes the construction of a peritoneal interposition flap (PIF) after completion of RARP and PLND.7 This PIF combines deep bilateral fenestration of the peritoneum with suture fixation of the bladder peritoneum to caudal parts of the paravesical fat (see Figure). The rationale of this surgical modification is to increase the drainage of lymphatic fluid from the pelvic lymphatic bed into the peritoneal cavity and to increase the resorptive peritoneal surface.

In their retrospective, single-center study, Lebeis et al demonstrated that the incidence of sLC was reduced from 11.6% to 0% if a PIF was performed.7 Further retrospective studies confirmed these findings, and a meta-analysis of these retrospective studies demonstrated a 77% reduction in the incidence of sLC (P < .001), although there was corresponding heterogeneity between studies.8

To translate this indirect evidence into direct evidence, randomized prospective trials have now been conducted to examine the effect of a PIF on overall lymphocele incidence (sLC) and on the incidence of sLC. The results of 4 studies have been published so far.9-12 While there was little difference between the studies in general, variations between the studies were predominantly related to the placement of fixation, number of sutures, and the type and period of follow-up.

The results of these studies are promising. In the German multicenter ProLy study, the construction of a PIF reduced the incidence of sLC from 8.1% to 3.3%
PERITONEAL INTERPOSITION FLAPS SUBSEQUENT TO ROBOT-ASSISTED RADICAL PROSTATECTOMY

Continued from page 10

Figure. To create bilateral peritoneal flaps, the edges of the bladder peritoneum are sutured to the endopelvic fascia (see Figure). ATP indicates arcus tendineus fasciae pelvis; PIF, peritoneal interposition flap.

(P = .03). Furthermore, the incidence of oLC was reduced by 33%, from 33% to 22%, demonstrating a highly statistically significant difference (P = .008). The follow-up period of the enrolled 475 patients included in this study was 90 days postoperatively, and the follow-up was performed sonographically, and the PIF was attached to the endopelvic fascia (see Figure).

The Czech PerFix study was performed in a single-center setting and evaluated data from a total of 245 men. The observation period was longest in this study, with a median of 595 days postoperatively. Comparable to the ProLy study, sLC incidence was significantly reduced in the intervention group from 11.5% to 2.4% (P = .011), while oLC incidence was also reduced from 41% to 22% (P = .002). In contrast to the other studies, the follow-up was performed by computed tomography, which might have been a reason for the high oLC incidences. Another difference was the location of peritoneal fixation, which was attached to the perist of the pubic bone.

The US single-center, single-surgeon PLUS study included a total of 216 men. While oLC incidences were significantly lower in the PIF group (3.6% vs 14.6%, P = .006), this difference was not observed for sLC (0.9% vs 0.9%, P = .999), but demonstrated exceptionally low incidences in both study groups. The follow-up period was 110 days and the follow-up was performed sonographically.

However, the results of the Pi-anoforte study contrast with the studies already mentioned. In this multicenter German study, no effect of PIF was observed. The incidence of sLC was not significantly different (8.3% vs 9.7%, P = .82), and although the incidence of oLC was lower in the intervention group, there was no significant difference between groups (17.6% vs 24.2%, P = .26). The follow-up period in this study was 90 days postoperatively and lymphocele occurrence was sonographically controlled. Differing sample sizes and exclusion rates may explain these varying results.

In conclusion, the results of surgical modification of RARP and PLND with PIF are promising at first glance, but meta-analyses are still pending. The results of a meta-analysis of the 4 prospective randomized studies are currently under review and are expected soon. Also expected are the results of the prospective, multicenter PELYCAN study, which will provide further clarity on the impact of a PIF on postoperative oLC and sLC incidences. If advantages for PIF are also found in both the meta-analysis and the PELYCAN study, future questions will have to examine the optimal PIF modification resulting in the greatest benefit for the patient.

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In mHSPC, NUBEQA is the only ARI approved in combination with docetaxel in mHSPC. NUBEQA in combination with docetaxel and ADT significantly extended OS beyond docetaxel + ADT; HR: 0.68; 95% CI: 0.57-0.80; P<0.0001.1,2

ARASENS Study Design: 1305 mHSPC patients on ADT* with docetaxel who received ADT within 12 weeks before study entry were randomized 1:1 and treated with concurrent 600 mg NUBEQA twice daily (n=651) or placebo (n=654) in a multicenter, double-blind, phase III trial. Treatment with NUBEQA or placebo continued until symptomatic progressive disease, change of antineoplastic therapy, or unacceptable toxicity. Concomitant docetaxel was administered at 75 mg/m² every 21 days for 6 cycles within 6 weeks of starting NUBEQA or placebo. OS was statistically significant for the NUBEQA arm vs placebo arm; HR: 0.68; 95% CI: 0.57-0.80; P<0.0001.1,2

In nmCRPC, NUBEQA + ADT reduced the risk of death by nearly a third vs ADT alone (OS was a secondary endpoint); HR: 0.69; 95% CI: 0.53-0.88; P=0.003. MFS was the primary endpoint.1,3

ARAMIS Study Design: 1509 nmCRPC patients on ADT* with a PSA doubling time of ≤10 months were randomized 2:1 to receive concurrent 600 mg NUBEQA twice daily (n=955) or placebo (n=554) in a multicenter, double-blind, phase III trial. Treatment continued until radiographic disease progression as assessed by CT, MRI, or bone scan by BICR, unacceptable toxicity, or withdrawal. MFS was statistically significant with a median of 40.4 months vs 18.4 months for placebo; HR: 0.41; 95% CI: 0.34-0.50; P<0.0001. The final analysis of OS was statistically significant vs placebo; HR: 0.69; 95% CI: 0.53-0.88; P=0.003. MFS was the primary endpoint and OS was a key secondary endpoint.1,3,4

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NUBEQA® (darolutamide) is an androgen receptor inhibitor indicated for the treatment of adult patients with:

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- Metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel

**INDICATIONS**

In ARAMES, serious adverse reactions occurred in 45% of patients receiving NUBEQA with docetaxel vs. 42% of patients receiving placebo with docetaxel. Serious adverse reactions in ≥2% of patients who received NUBEQA with docetaxel included febrile neutropenia (6%), decreased neutrophil count (2.8%), musculoskeletal pain (2.6%), and pneumonia (2.6%). Fatal adverse reactions occurred in 4% of patients receiving NUBEQA with docetaxel vs. 4% of patients receiving placebo with docetaxel. Fatal adverse reactions in patients who received NUBEQA included COVID-19/COVID-19 pneumonia (0.8%), myocardial infarction (0.3%), and sudden death (0.3%). The most common adverse reactions (≥10% with a ≥2% increase over placebo with docetaxel) were constipation, decreased appetite, rash, hemorrhage, increased weight, and hypertension. The most common laboratory test abnormalities (≥30%) were anemia, hyperglycemia, decreased lymphocyte count, decreased neutrophil count, increased AST, increased ALT, and hypocalcemia. Clinically relevant adverse reactions in <10% of patients who received NUBEQA with docetaxel included fractures, ischemic heart disease, seizures, and drug-induced liver injury.

**Drug Interactions**

Effect of Other Drugs on NUBEQA – Combined Pgp and strong or moderate CYP3A4 inducers decrease NUBEQA exposure, which may decrease NUBEQA activity. Avoid concomitant use.

Combined Pgp and strong CYP3A4 inhibitors increase NUBEQA exposure, which may increase the risk of NUBEQA adverse reactions. Monitor more frequently and modify NUBEQA dose as needed.

Effects of NUBEQA on Other Drugs – NUBEQA inhibits breast cancer resistance protein (BCRP) transporter. Concomitant use increases exposure (AUC) and maximal concentration of BCRP substrates, which may increase the risk of BCRP substrate-related toxicities. Avoid concomitant use where possible. If used together, monitor more frequently for adverse reactions, and consider dose reduction of the BCRP substrate.

NUBEQA inhibits OATP1B1 and OATP1B3 transporters. Concomitant use may increase plasma concentrations of OATP1B1 or OATP1B3 substrates. Monitor more frequently for adverse reactions and consider dose reduction of these substrates.

Review the Prescribing Information of drugs that are BCRP, OATP1B1, and OATP1B3 substrates when used concomitantly with NUBEQA.

*Concomitant GnRH analog or prior bilateral orchietomy.

**References:**

1. NUBEQA (darolutamide) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc.; August 2022.

**IMPORTANT SAFETY INFORMATION**

**Warnings & Precautions**

**Drug Interactions**

**Important Safety Information**

Visit NUBEQAhcp.com
INDICATIONS AND USAGE: NURJE is indicated for the treatment of adult patients with:

- non-metastatic castration-resistant prostate cancer (mCRPC)
- metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation.

WARNINGs AND PRECAUTIONs: 6.

6.1 Ischemic Heart Disease

Ischemic heart disease, including tachyary, occurs in patients receiving NURJE.

In a randomized study of 1,274 patients with mHSPC (ARIS), ischemic heart disease occurred in 32% of patients receiving NURJE and 25% receiving placebo with Grade 3-4 events in 7.1% and 4.4%, respectively. Ischemic events led to death in 0.9% of patients receiving NURJE and 0.6% receiving placebo.

In a randomized study of 1,641 patients with mCRPC (ARIMIS), ischemic heart disease occurred in 6% of patients receiving NURJE and 4.5% receiving placebo with Grade 3-4 events in 4% and 1.5%, respectively. Ischemic events led to death in 0.5% of patients receiving NURJE and 0.1% receiving placebo.

Table 6: Laboratory Test Abnormalities (3.4%) in the ARIMIS study

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<tbody>
<tr>
<td>Hemoglobin decreased</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
</tr>
<tr>
<td>Platelet count decreased</td>
</tr>
<tr>
<td>AST increased</td>
</tr>
<tr>
<td>ALT increased</td>
</tr>
<tr>
<td>Bilirubin increased</td>
</tr>
</tbody>
</table>

Note: The denominator used to calculate the rates was obtained from the number of patients with a baseline and at least one post-baseline value.

6.2 Lactation

The safety and efficacy of NURJE have not been established in breastfeeding women. It is not known whether NURJE will appear in human milk. The effect on the nursing child, or the effect on milk production, is unknown.

6.3 Females and Males of Reproductive Potential

Growth suppressors may reduce the number of sperm produced or reduce the number of ovulatory cycles. Growth suppressors are not known to be effective in preventing pregnancy.

6.4 Pediatric Use

Safety and effectiveness of NURJE in pediatric patients have not been established.

6.5 Geriatric Use

NURJE is not recommended for use in patients aged 65 years and older, and 75% were 75 years or over. The 65% were patients who received NURJE in ARIMIS. 6% of patients were 65 years or older, and 6% were 75 years or over. No overall differences in safety or efficacy were observed between these patients and younger patients in both studies.

6.6 Renal Impairment

Patients with severe renal impairment (GFR 30-50 ml/min) who are not on haemodialysis have a higher risk of NURJE due to reduced efficacy. Malignant tumors may decrease the effectiveness of NURJE.

NURJE is not recommended for use in patients with moderate renal impairment (GFR 15-30 ml/min) due to reduced efficacy. Malignant tumors may decrease the effectiveness of NURJE.

NURJE is not recommended for use in patients with severe renal impairment (GFR <15 ml/min) due to reduced efficacy. Malignant tumors may decrease the effectiveness of NURJE.

7. INTERACTIONS

7.1 Drug Interactions

NURJE is not known to be a substrate, inducer, or inhibitor of CYP3A4, CYP1A2, or CYP2C19. Therefore, coadministration with NURJE is not expected to have a significant effect on the pharmacokinetics of NURJE.

Commonly used concomitant medications include:

- Antihypertensives
- Statins
- Antidiabetics
- Antithrombotic agents
- Anti-inflammatory agents

Inhibition of CYP3A4 by NURJE is not expected to affect the pharmacokinetics of concomitantly administered CYP3A4 substrates.

NURJE is not expected to affect the pharmacokinetics of concomitantly administered CYP3A4 substrates.

Treatment with reduced efficacy due to reduced renal function. Malignant tumors may decrease the effectiveness of NURJE.

NURJE is not recommended for use in patients with severe renal impairment (GFR <15 ml/min) due to reduced efficacy. Malignant tumors may decrease the effectiveness of NURJE.

NURJE is not recommended for use in patients with moderate renal impairment (GFR 15-30 ml/min) due to reduced efficacy. Malignant tumors may decrease the effectiveness of NURJE.

NURJE is not recommended for use in patients with severe renal impairment (GFR <15 ml/min) due to reduced efficacy. Malignant tumors may decrease the effectiveness of NURJE.
Randomized Controlled Trials to Inform Prostate Biopsy Debate

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Transrectal prostate biopsy (TR-Bx), a long-held standard for prostate cancer detection, is among the most common urological procedures worldwide. The procedure has undergone several refinements over the last 3 decades to address 2 major concerns, namely the sampling error that is inherent to the ultrasound-guided systematic (random) biopsy and infectious complications. The integration of prebiopsy multiparametric MRI into the diagnostic pathway and the subsequent MRI-targeted TRBxs has significantly reduced the sampling error and improved the detection of clinically significant prostate cancer.1,2

More concerning than the diagnostic yield are the reports demonstrating rising rates of post–TR-Bx infections. As many as 30%-50% of Escherichia coli isolates, the most common organism reported in postbiopsy infections, may be resistant to fluoroquinolones and other commonly used antibiotics.3,4 Consequently, some centers have reported postbiopsy infection rates of >10% while others report a 2-fold to 4-fold increase in infectious complications.5,6

Several strategies have been employed to decrease the risk of infectious complications. The antibiotic-based preventive strategies have included the use of broad-spectrum antibiotics, longer antibiotic course, antibiotics targeted to rectal cultures, and multiagent augmented antibiotic prophylaxis.7,9 The nonantibiotic preventive strategies have focused on antiseptic measures including cleansing the biopsy needle after each sample using formalin or alcohol, and rectal preparation using chlorhexidine, antimicrobial lubricants, or povidone-iodine solution.10 Of the nonantibiotic preventive measures povidone-iodine rectal preparation appears most promising in reducing infectious complications without escalating antibiotic usage.11

Primarily due to the concerns surrounding infectious complications, experts have proposed the utilization of transperineal prostate biopsy (TP-Bx) as the preferred alternative to the TR-Bx procedure.12 Several observational studies have indicated that TP-Bx is associated with a lower risk (~1%) of postbiopsy infections,13,15 and improved detection of clinically significant prostate cancer. The European Association of Urology guidelines recommend abandoning TR-Bx and switching to TP-Bx. Despite the promising results from several observational studies

Table. Selected Randomized Controlled Trials Comparing Transrectal and Transperineal Prostate Biopsy Procedures

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Study title</th>
<th>Start datea</th>
<th>Enrollment</th>
<th>Hypothesis</th>
<th>Study population</th>
<th>Participants (N)</th>
<th>Primary outcome</th>
<th>Secondary outcomesb</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT04081636</td>
<td>Prostate Biopsy Efficacy and Complications (ProBE-PC study)</td>
<td>9/2/2019</td>
<td>Completed</td>
<td>TP-Bx is superior to TR-Bx in reducing infectious complications</td>
<td>All men undergoing prostate biopsy (biopsy-naive and previous negative)</td>
<td>774</td>
<td>Rate of infectious complications</td>
<td>Clinically significant prostate cancer detection rate; hemorrhagic complications; tolerability, pain scores; patient-reported urinary and sexual function; cost-effectiveness</td>
<td>Albany Medical Center</td>
</tr>
<tr>
<td>NCT04843566</td>
<td>Evaluation of Transperineal Biopsy Under Local Anesthesia</td>
<td>3/22/2021</td>
<td>Recruiting</td>
<td>MRI-targeted TR-Bx compared to MRI-targeted TR-Bx has a much lower risk of infection</td>
<td>Biopsy-naive men</td>
<td>400</td>
<td>Change in infection-related adverse events</td>
<td>Pain and discomfort; detection of clinically significant prostate cancer</td>
<td>Weill Medical College of Cornell University</td>
</tr>
<tr>
<td>NCT04815876</td>
<td>Transperineal vs Transrectal MRI-targeted Prostate Biopsy</td>
<td>6/24/2021</td>
<td>Recruiting</td>
<td>MRI-targeted TR-Bx compared to MRI-targeted TR-Bx has a much lower risk of infection</td>
<td>Men on active surveillance; men with prior negative biopsy</td>
<td>1,302</td>
<td>Change in infection-related adverse events</td>
<td>Pain and discomfort; detection of clinically significant prostate cancer</td>
<td>Weill Medical College of Cornell University</td>
</tr>
<tr>
<td>NCT05179694</td>
<td>Transrectal Biopsy vs Local Anesthetic Transperineal Biopsy in Evaluation (TRANSLATE) of Men With Potential Clinically Significant Prostate Cancer</td>
<td>12/3/2021</td>
<td>Recruiting</td>
<td>Superior detection rate of clinically significant prostate cancer with TP-Bx</td>
<td>Biopsy-naive men</td>
<td>1,042</td>
<td>Detection of clinically significant prostate cancer</td>
<td>Infectious complications; health-related quality of life; tolerability and pain; patient-reported complications; cost-effectiveness</td>
<td>University of Oxford</td>
</tr>
<tr>
<td>NCT05069584</td>
<td>Transperineal Fusion Biopsy Versus Transrectal (PERFECT trial)</td>
<td>1/17/2022</td>
<td>Completed</td>
<td>Targeted TP-Bx is noninferior to targeted TR-Bx diagnostic efficiency</td>
<td>Biopsy-naive men, with PI-RADS 4-5 lesion on MRI</td>
<td>270</td>
<td>Detection of clinically significant prostate cancer</td>
<td>None listed</td>
<td>GCS Ramsay Santé Pour l’Enseignement et la Recherche</td>
</tr>
</tbody>
</table>

Abbreviations: MRI, magnetic resonance imaging; PI-RADS, Prostate Imaging Reporting & Data System; TP-Bx, transperineal biopsy; TR-Bx, transrectal biopsy.

Data were obtained from www.clinicaltrials.gov on July 1, 2023.

aStart dates are listed in chronological order.

bClinically significant prostate cancer is defined as Gleason score ≥7 or grade group ≥2.
“Primarily due to the concerns surrounding infectious complications, experts have proposed the utilization of transperineal prostate biopsy (TP-Bx) as the preferred alternative to the TR-Bx procedure.”

TP-Bx approaches. With an estimated 2 million prostate biopsy procedures performed annually in North America and Europe, a major shift in clinical practice, such as abandoning a procedure, must be guided by strong comparative effectiveness studies. To date, there is a distinct lack of randomized clinical trials (RCTs) directly comparing the complications and efficacy of TR-Bx and TP-Bx procedures.

Until recently, RCTs comparing the 2 biopsy procedures were deemed unnecessary. Fortunately, a number of investigators and funding agencies have recognized this gap in scientific evidence. At present, several large RCTs have been initiated that are well powered and specifically designed to compare the infectious complications and/or diagnostic efficacy of the 2 biopsy procedures. A few of the selected RCTs are listed in the Table. With the recognition of the lower quality of existing evidence in the European guidelines, and the stated desire to incorporate future RCT data in the American guidelines, the need for strong evidence has taken its rightful place in the prostate biopsy debate.

“With the recognition of the lower quality of existing evidence in the European guidelines, and the stated desire to incorporate future RCT data in the American guidelines, the need for strong evidence has taken its rightful place in the prostate biopsy debate.”

Applications Now Being Accepted for AUA’s Next Research Chair

The AUA is currently seeking a highly-qualified active member to fill the position of Research Chair-elect beginning June 2024. A job description along with information about compensation, time commitments and travel requirements are available online at AUAnet.org/ResearchChair.

Deadline to receive applications is October 8, 2023.


A Urologist’s Perspective: A Window Into Baseball

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University of Florida Health System, Gainesville

The concept for an article recognizing unique and famous patients from a urologist’s perspective grew out of a conversation I had at the recent AUA meeting in Chicago. Kevin Loughlin, a longtime friend and former co-AUA Board Member, as well as a lifetime Boston Red Sox fan, knew of my friendship with former star player Ted Williams that grew out of a doctor-patient relationship. He suggested that I write an article about that experience and also suggested that many urologists have had unique and special relationships with well-known and in some cases famous patients. Joe Kaufman was known as the urologist to the Hollywood stars. Former AUA President Bill Bohnert once told me about an insightful and hilarious patient encounter with former US presidential candidate Barry Goldwater. My forever friend and coresident, Mike Wehle, befriended the Reverend Billy Graham as a result of a patient relationship. Hopefully, this will mark the beginning of many similar shared stories about those special relationships. Of note in this case, the first time I met our current AUA Secretary, Dave Penson, the majority of our conversation was about our shared reverence for Ted Williams. I think it is the main reason he still likes me.

I have a friend who refers to me as a raconteur, a storyteller. I want to share with you the story of a special, meaningful, and privileged doctor-patient relationship with another storyteller.

The signed Sports Illustrated cover on my office wall states, “To my doctor and friend, signed Ted Williams.” For those who might not know, either because it was too long ago or because they are not baseball or sports fanatics, Ted Williams of Boston Red Sox fame is widely regarded as the best hitter in the history of baseball. Certainly, he is remembered as the last hitter to hit over .400 in a single season. His on-base percentage of .482 is the highest of all time. By the way, Ted was one of a handful of athletes to be inducted into 2 sports Halls of Fame: baseball and fishing. He was also inducted into the Marine Corps Hall of Fame, so really 3 in total.

Ted Williams, also known as “Teddy Ballgame,” “The Kid,” and “The Splendid Splinter,” graced me as my patient and friend for over a decade. He was my window into a bygone era of a sport that captured the imagination of both the young and the old for generations. Much has been written about his career, his teammates, his...
relationship with the press, and his time in proud service to his country as a Marine pilot.

I want to share some personal insights and memories that made my relationship with Ted Williams very special to me. In so doing, I want to emphasize the special opportunity and privilege that we have, as urologists, to be part of our patients’ lives and how those relationships, in turn, impact us.

I clearly remember the first time I was face to face with Ted Williams. He was very recognizable: tall, broad-shouldered, and imposing. He seemed a little suspicious and certainly not initially friendly. I shared with him my medical opinion and carefully described the pending procedure, including the associated discomfort, after which he said, “It was exactly what you told me it would be.” I had earned his trust, which became an important part of our friendship.

Initially, Ted and I maintained in-office visits that produced some understandable fanfare. To that point, we quickly morphed to home visits. Those home visits then became routine multi-hour conversations sitting across from him at his kitchen table. Ted was, as far as I am concerned, the ultimate storyteller. It was, for me, a once-in-a-lifetime opportunity to gain access to a special era of baseball and really to life in general through the eyes of my new friend.

My children knew something about my famous patient but did not truly understand altogether why he was famous. Regardless, when Ted called and asked me to come over to execute some legal documents one Christmas Eve, they were curious enough to want to come along with me to meet him. I think they struggled to discern the famous part from the old guy sitting at the kitchen table in his underwear. Maybe it sunk in some when the sitting President of the United States, George H. W. Bush, called to personally wish Ted a Merry Christmas. President Bush subsequently presented Ted with the Presidential Medal of Freedom, which is the highest civilian award bestowed by the United States government.

The hospital used an alias to respect Ted’s privacy. It was Ted Rivers. On Christmas Day, the hospital operator called to inform me that Ted Rivers was in the hospital and was asking to see me. Ted Rivers? “I don’t know Ted Rivers,” I said. After multiple failed attempts to make me understand, the operator finally blurted, “It’s Ted Williams.” “Oh. Ok. I will be right there.” It was the day after visiting him with the kids. He had fallen and broken his hip. When I got to his room, he was squinting, eyes closed in pain. I quietly spoke his name. He opened his eyes and the first thing he said to me was, “Oh, Doc, you’re here. How are the kids?” Don’t ever tell me Ted Williams didn’t have a big heart.

Through Ted, I met many other famous people. Ted had a baseball museum in the community where we lived. There was an annual induction into his hitter’s hall of fame. Every baseball legend you could imagine clamored to be present. Willie Mays, Stan Musial, Frank Robinson, among others. The master of ceremonies for years was Bob Costas and later Tommy Lasorda. One year I sat with my son as guests of Ted in the front row with Michael Bolton singing the national anthem and George and Barbara Bush sitting directly in front of us. As we exited, I lost track of my young son for an instant only to find him in a conversation with Micky Mantle. Ted was very proud of his relationships within baseball, including his teammates and the other stars of his era. I remember clearly the 1999 Major League Baseball All-Star Game held in Boston. Ted was to be individual-

ly honored. He was in a wheelchair by that time. All-Star players from both leagues hovered to be close to him. No one wanted to leave his side. The actual start of the game was delayed 15-20 minutes because of that spontaneous tribute. However, I think the accomplishment that Ted was most proud of was his 5-year military service in both World War II and the Korean War as a Marine pilot. He served as John Glenn’s wingman in Korea. John frequently visited Ted at his home, which provided me with an opportunity to meet him as well.

My wife, Leah, is a big tennis fan (Ted secured tickets for us to center court Wimbledon in 1997) but not a big sports fan in general. However, she does have a connection to baseball. Her uncle was Augie Donatelli, a famous National League umpire who, by the way, was on the front cover of the original edition of Sports Illustrated. I asked Ted if he knew him. As it turned out, Augie called a third strike on Ted in a Chicago All-Star Game. Ted knew the strike zone probably better than anyone. Two inches up and off the plate he said. That was no damn strike he exclaimed. Unlike the press, Ted prioritized his relationships with the players, which included the umpires. Regardless, he reiterated, “Worst strike ever called on me.” He told me he harbored that thought for years. Then one day, during spring ball in Arizona decades later and when he was the Texas Rangers manager, he ran into Augie and several other former umpires in a bar in Phoenix. They invited him to join, and after a pregnant silence Augie admitted to Ted that he had also harbored a similar thought for decades about that All-Star Game called strike, knowing that it was “the worst strike I ever called.” Ted was vindicated and they shared a laugh and a beer.

Ted struggled throughout his career with the press and, in general, did not trust them. That strained relationship surfaced late in his life as well. When Joe DiMaggio died in Florida the press asked Ted who was the better player. Joe had prevailed several times over Ted for the American League MVP award, which Ted also won twice. Ted answered honestly that Joe was the better player but that he was the better hitter. True. However, the press roasted him for that comment.

I dealt with the press as well after Ted’s death. The well-publicized controversy at his death was over a family decision to permanently preserve his body. Television station WBZ from Boston did a live interview with me a week after his death. What I thought was going to be a tribute to Ted and his life, including his humanitarian impact through the Jimmy Fund, turned out to be a sensational inquisition about the status of his body. I terminated the interview.

Near the end of Ted’s life, I was standing at the hospital elevator when a nurse from the emergency room saw me and stated, “I hear you know Ted Williams.” I said yes, and why did she ask? She said that her mom cleaned his house, and when she picked her up the other day, Mr Williams asked her if she knew me. Of course, she answered, everyone knows Dr Stringer. She hesitated to tell me what Ted then said. Eventually she shared, “He said that you were a great [expletive] guy.” A high compliment and one that I cherish.

Ted Williams and I started our relationship as doctor to patient, which included over time his signature on his death certificate. Without a doubt, the cherished memories of our friendship live on.
Across surgical disciplines, studies have consistently shown that outpatient surgeries result in comparable or even improved patient outcomes, including reduced complication rates, shorter hospital stays, faster recovery, and increased patient satisfaction.\(^1\) The shift toward outpatient surgery has been driven by factors such as cost-effectiveness, improved surgical techniques, enhanced recovery protocols, and advancements in anesthesia and pain management.

In 1996, Klein et al described implementation of a protocol which decreased the median length of stay from 7 to 2 days following radical prostatectomy while maintaining a high level of patient satisfaction.\(^2\) The shift toward outpatient surgery has been driven by factors such as cost-effectiveness, improved surgical techniques, enhanced recovery protocols, and advancements in anesthesia and pain management.

Almost 20 years later, Abaza et al described implementation of a same-day discharge (SDD) protocol.\(^1\) Starting in 2016, this option was discussed preoperatively with patients subsequently deciding after surgery whether to go home or stay overnight. They found that among 500 consecutive patients the overall rate of SDD was 49.2%, but notably increasing to 65% in the last 100 patients (see Figure). There was no increase in readmission rate (0.4% for SDD vs 2.8% for admitted, \(P = .68\)). Complication rates were lower in SDD patients (4.4% vs 9%, \(P = .05\)) with fewer Clavien III complications (0.8% vs 4%, \(P = .036\)). The major factor associated with patients electing SDD was operative end time. Nearly 70% of first-start patients chose SDD compared to 2.5% of third-start patients (ending late afternoon).

A multi-institutional study in France found that planned SDD was successful in 95.8% of patients (n=358) undergoing same-day robot-assisted laparoscopic prostatectomy.\(^3\) On multivariable analysis, factors associated with failure were performance of a pelvic lymph node dissection and blood loss. There was significant surgeon and site variability with SDD representing 15%-60% of the surgeon robot-assisted radical prostatectomy cohort and 10%-30% of the center robot-assisted radical prostatectomy cohort. However, like Abaza et al’s initial study, rates of SDD continuously increased over the study time period, ultimately approaching 60% at some centers.

COVID-19 accelerated the move toward SDD. A retrospective analysis of 2 large Northeastern hospitals found that SDD increased from 4.4% at the end of the fourth quarter of 2020 to 45% by the second quarter of 2022.\(^4\) The authors found no difference in patient characteristics between the 2 groups (SDD and overnight admission). Similar to Ploussard et al’s findings,\(^5\) factors associated with SDD were institution and surgeon volume (higher-volume surgeons were predictive of SDD).

Szymanski et al reported that, between January 2019 and December 2021, 139/497 (28%) of prostatectomies completed by 4 fellowship-trained urologic oncologists at a single institution were done...
as SDD. There were no significant clinidemographic features bev- between the inpatient and outpatient groups. Increased operative time and blood loss were the only factors associated with admission. Notably surgeon level variation was not analyzed. Importantly, the authors found that there was a higher rate of readmission (5% vs 0%, \( P = .007 \)) and emergency department visits (mean 0.15 vs 0.05, \( P = .02 \)) among patients who were admitted. Overall complication rate was 72% vs 19.8% in the inpatient vs outpatient group. SDD also did not increase clinical staff workload, with no difference in number of phone calls to clinic or number of electronic health record messages.

Moving from selective to universal SDD, between October 2021 and October 2022, Abaza et al reported a 99% success rate in 352 consec- tive radical prostatectomy cases with a 2.5% readmission rate. Cases were done in either an ambulatory surgery center without overnight stay capability (n=162) or a hospital (n=197), determined by patient risk factors [BMI, severe cardiac disease, etc] and insurance coverage.

In summary, the existing data show that same-day prostatectomy is safe and does not result in higher readmission rates or increased clin- ical burden. The critical compo- nent of SDD acceptance is preop- erative patient counseling. Notably this is discussed extensively in the papers by Litwin and Klein et al as fundamental to patient accep- tance of decreased length of stay in the open surgery era. Likewise, Abaza et al describe the critical importance of patient education, noting that over time the patients became more comfortable as they could explain that most patients elected SDD without experiencing any unexpected issues. Similarly, Ploussard et al reported 76% ad- herence with SDD protocols when discussed at the preoperative visit. We observed a similar trend at our institution. In 2021 we began offering the option of SDD to patients. Once we recognized the safety and improvement in patient recovery, it became our standard of care. Over a 1-year period between May 2022 and May 2023, 86% of our prostatectomies were successfully done as SDD.

Future studies demonstrating cost- effectiveness, patient satisfaction/ return to work, and/or improved outcomes are likely needed for SDD to be considered the standard of care. However, the literature supports the safety and feasibility of SDD, and surgeons should feel confident in discussing the option with their patients.


PROSTATE CANCER

Early Detection of Prostate Cancer: Highlights From 2023 AUA/Society of Urologic Oncology Guidelines

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Given continued advances in prostate cancer early detection—from imaging to diagnostic approaches used for risk stratifi- cation—updates to the existing framework to guide clinical decision-making were needed. The AUA and Society of Urologic Oncology (SUO) issued new guidelines published in The Journal of Urology® in July 2023, with a specific focus on these domains.

The new guidelines are based on the expert panel’s interpretation of a comprehensive systematic review of the existing literature, with the stated goal of identifying clinically significant cancer while minimizing harms. Below, we provide a synopsis of notable changes in the new guidelines compared to those previously published in 2013.

Part I: Screening

In contrast to a purely age-based approach to PSA-based screening as recommended in the 2013 guideline, the current version em- phasizes the importance of shared decision-making for all patients in whom screening would be appropriate. Further, given additional results from long-term follow-up of the European Randomized Study of Screening for Prostate Cancer and Göteborg randomized prostate cancer screening trials showing a mortality benefit to PSA-based screening and limited data suggest- ing utility of other biomarkers or imaging as first-line tests, PSA is still recommended as the first screening test.

In those at average risk, it is now stated that PSA testing can be offered starting at age 45, compared to the initial recommendation in 2013 against routine screening in men 40-54 years. While the 2013 guidelines recommend- ed an individualized approach to PSA testing in patients aged 40-54 years with high risk factors (Black race, strong family history), this statement was amended to include a strong recommendation for screening beginning at 40-45 years for this population. Patients with germline mutations in BRCA2 or mismatch repair genes (MSH2, MSH6) were also recommended to undergo early screening because

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Prostate Biopsy
Part II: Considerations for Prostate Biopsy

EARLY DETECTION OF PROSTATE CANCER
Continued from page 20

of high risk for detection of aggressive tumors.5,6 With regard to frequency of screening, the updated guidelines recommend screening every 2 to 4 years for patients aged 50-69 years, with potential for personalization based on shared decision-making.

Digital rectal exam (DRE) is now considered optional as a complementary screening modality to PSA testing. Results from the PROBASE trial of over 40,000 men showed a low rate of cancer detection using DRE with delayed PSA testing.7 However, in the setting of elevated PSA ≥2 ng/mL, the guidelines state clinicians should strongly consider DRE to establish the risk of clinically significant cancer. Lastly, the new guidelines also include a statement suggesting risk calculators may be used to aid in shared decision-making, with the caveat that these tools have substantial variability with wide population-based averages and uneven calibration.

Part II: Considerations for Prostate Biopsy

Due to the widespread availability and utility of prostate multiparametric MRI (mpMRI) in modern management algorithms, the new guidelines recommend a defined role for mpMRI. Based on results from the PRECISION study showing increased detection of clinically significant cancer with reduced detection of clinically insignificant disease with MRI-targeted vs systematic biopsy, the panel provided a conditional recommendation for prebiopsy mpMRI.8 Additional randomized trial results have suggested noninferiority of an MRI-targeted biopsy-only approach to screening for prostate cancer.9,10 However, in those with negative mpMRI results and elevated risk, systematic biopsy is still recommended because of the risk of missing clinically significant cancers with negative MRI alone.11 In those with suspicious lesions on mpMRI, it is recommended that targeted biopsy be performed. However, the role of the addition of systematic biopsy in this setting is debatable, with the tradeoff being increased detection of low-risk cancers vs missed clinically significant cancers without systematic biopsy.12,13

The guidelines also address the numerous serum-, urine-, and tissue-based biomarkers available for identifying patients for prostate biopsies. However, they are recommended only in scenarios in which test results would influence decision-making regarding need for biopsy. While various biomarkers have documented utility in this setting and ability to reduce unnecessary biopsies, no specific biomarker is endorsed as no comparative studies are available. Nonetheless, these tools are available for use in the initial and repeat biopsy settings (see Figure). In the setting of a prior negative biopsy, the panel recommends use of a risk assessment approach that combines patient factors, PSA, mpMRI results, and biomarker tests as needed for reevaluation.

With regard to biopsy technique, the panel recommends either a transrectal or transperineal approach, citing similar cancer detection rates with both techniques. While some evidence suggests superior safety of transperineal biopsy vs systematic biopsy, the panel did not recommend preferential use of the transperineal technique as the data are still mixed.14,15

Key Differences From the European Association of Urology and National Comprehensive Cancer Network Guidelines

Both the European Association of Urology (EAU) guidelines and the National Comprehensive Cancer Network (NCCN) guidelines still recommend performing DRE in addition to PSA for screening. Despite the low sensitivity and specificity of DRE, the EAU guidelines state, “Men requesting an early diagnosis should be given a PSA test and undergo a DRE,” as in 18% of cases prostate cancer is detected by suspect DRE alone, and an elevated PSA with...
abnormal DRE doubles the risk of positive prostate biopsy. While the AUA/SUO guidelines state that mpMRI may be used prior to initial biopsy, this is the recommended practice by the EAU and NCCN guidelines, with a “strong” strength rating. This is complemented with the recommendation by the EAU that prostate biopsy can be omitted in patients with negative mpMRI, albeit this was given a “weak” strength rating. In this scenario, AUA/SUO guidelines recommend performing targeted biopsy with lesions more than 5 mm in diameter on mpMRI with targeted biopsy only with a positive mpMRI (Prostate Imaging Reporting & Data System 3 or higher) result, whereas AUA/SUO and NCCN guidelines state that systematic biopsy also may be considered and is preferred. Given studies showing improved detection of clinically significant cancer and reduction in infectious complications with targeted transperineal biopsy, EAU guidelines recommend a transperineal over transrectal approach. However, the NCCN states transrectal or transperineal approaches can be used.

Future Directions

Future iterations of these guidelines will seek to address other evolving areas in prostate cancer detection to assist clinicians. For example, the panel will evaluate forthcoming studies on comparative effectiveness of different biomarkers and their sequencing with other clinical tools, such as mpMRI, to make recommendations about using the appropriate biomarker for each clinical scenario. Further, recommendations regarding utility of prostate-specific membrane antigen positron emission tomography/CT imaging and specialized recommendations for diverse patient populations are needed. Nonetheless, the update by the AUA/SUO was a needed renewal given the evolving landscape of prostate cancer screening and early detection.

Disparities in Prostate Cancer: Nature or Nurture or Both?

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September is a meaningful month for several reasons. I can recall my excitement as a child energized from the beginning of the academic school year. My mother was born in September and I can’t tell you how many odd jobs I’ve worked to save money to purchase a gift for her on the morning of her birthday. I started off as an aspiring carpenter before working as a gardener, telemarketer, and night shift Philadelphia Tastykake factory worker. If I called you trying to get you to expand your basic cable service or asking you to answer survey questions during the 1990s, please forgive me!

As a urologist in training, September became even more meaningful after the United States Senate passed Senate Resolution 138 on August 3, 2001, designating the month of September as National Prostate Cancer Awareness Month. Since then, I have used September as a marker of where we are as a field regarding prostate cancer disparities. I have long been aware that I carry 2 risk factors for the development of prostate cancer, as a Black male whose father succumbed to prostate cancer. One of the things I was taught early on during my training was that Black men had a higher risk of prostate cancer and that outcomes were typically worse compared to other groups. Interestingly, my lived experience with my father, I often wondered whether disparities in prostate cancer were rooted in nature, nurture, or both.

The number of investigators in our field working to address this issue has multiplied over the years. A recent PubMed search for “Prostate Cancer Disparities” yielded 1,983 results. The yearly output has increased from 6 in 2001, the year that I graduated from medical school, to 236 in 2022. This reflects a greater focus on disparities and what they mean for not only the Black community, but other communities underrepresented in medicine.

We have made significant progress in reducing cancer mortality in the United States over the last 25 years. Investigators from the American Cancer Society shared our progress in reducing cancer mortality in the United States by congressional district from 1996-2003 compared to 2012-2020. Prostate cancer death rates substantially declined in each congressional district with relative decline ranging from 25% to 68%. Among Black males, congressional districts with the highest death rates were scattered across the United States during both periods. However, there now appears to be a greater concentration in the South. Prostate cancer outcomes have more than we previously thought to do with factors unrelated to nature.

One of the most interesting reports I have read over the last year was a manuscript published in Journal of Clinical Oncology titled “Racism Does Not Cause Prostate Cancer, It Causes Prostate Cancer Death.” The authors highlighted evidence from epidemiological and genetic studies that the increased incidence of prostate cancer in Black men is rooted in genetics. Nevertheless, the effects of racism influence the chances that someone will die as a result.

Disparities in prostate cancer exist among men who are part of the Hispanic, American Indian, and Alaskan Native communities. They often present with more advanced disease, have lower rates of definitive treatment, suffer higher mortality, and reside in areas with less access to specialty care. Racial inequities have been shown to exist in the surgical care of Medicare beneficiaries with localized prostate cancer. A recent meta-analysis revealed that Black and Hispanic men remain under-represented in prostate cancer clinical trials. Advocacy remains one of the keys to addressing disparities in prostate cancer.

Advocacy at the local, regional, and national level can have a profound impact on disparities in not only prostate, but other urological conditions.

“Prostate cancer outcomes have more than we previously thought to do with factors unrelated to nature.”

At the time of BCR in nmCSPC, PSA doubling time (PSADT) has been shown to be one of the most reliable indicators of the risk for further progression.¹,²

Following definitive therapy, a rapid PSADT ≤9-12 months indicates an increased risk of prostate cancer-related morbidity and mortality.¹,³

American Urological Association (AUA) Guidelines and NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) offer direction for understanding BCR following radical prostatectomy and radiation therapy.⁴,⁵