American Urological Association

AUANews

SEPTEMBER 2023

VOLUME 28 | ISSUE 9

AUANews.net

THE OFFICIAL NEWSMAGAZINE OF THE AMERICAN UROLOGICAL ASSOCIATION

– FOCUS ISSUE –

Prostate Cancer

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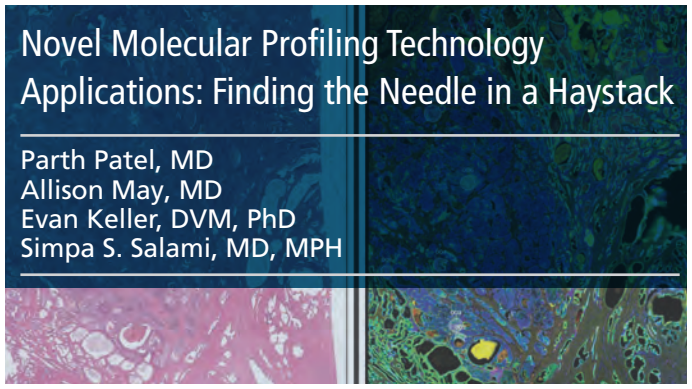

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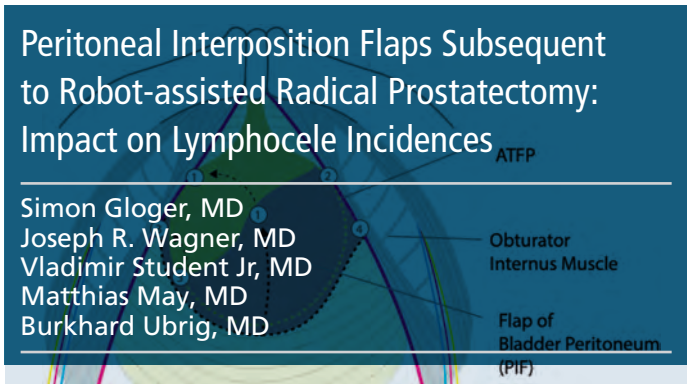

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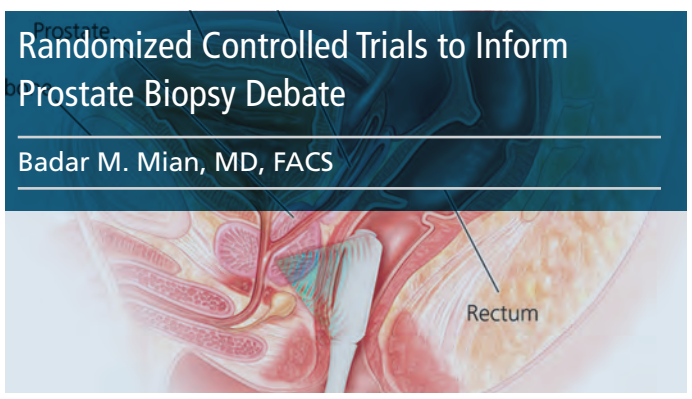

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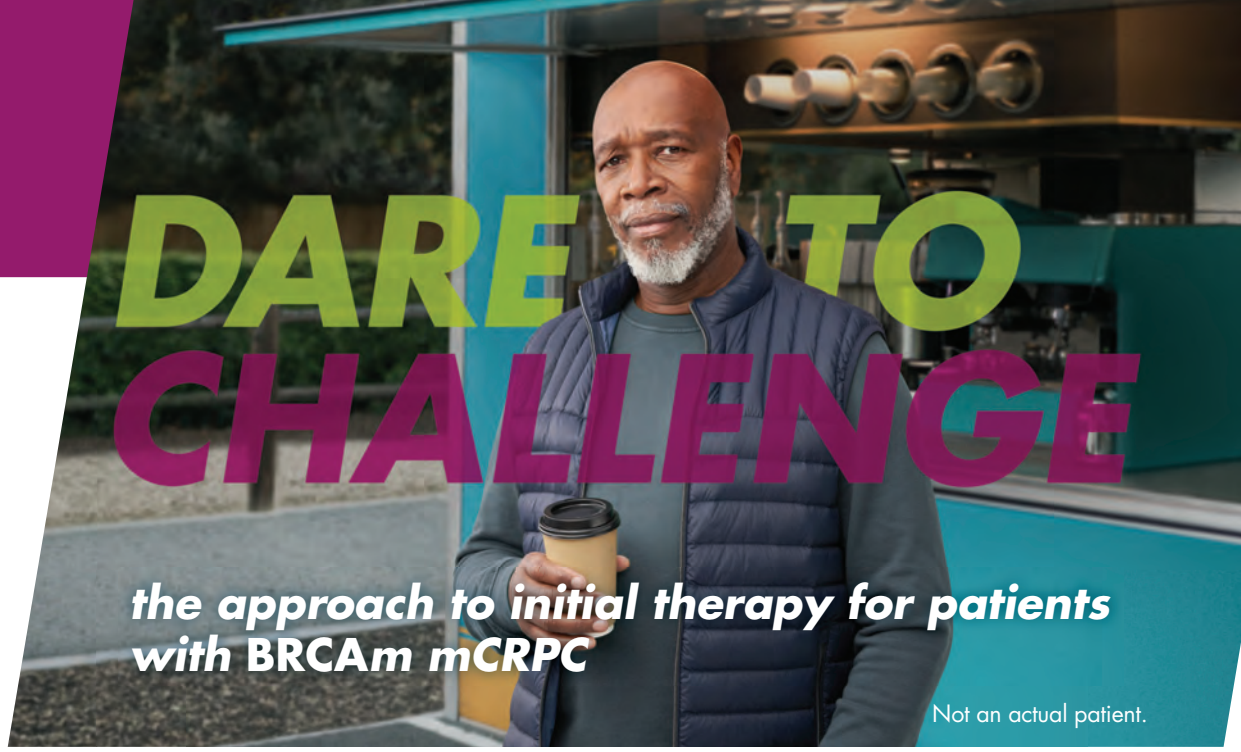


NOW APPROVED

LYNPARZA: the FIRST and ONLY PARPi approved in combination with abiraterone plus prednisone or prednisolone (abi/pred) as initial therapy for *BRCAm* mCRPC[1-4]

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 (*BRCA*m) 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[1,5]

- PROpel was a randomized, double-blind, placebo-controlled, multicenter, phase 3 trial
- ITT population (N=796): mCRPC with or without HRR mutations
  - **FDA approval of LYNPARZA + abi/pred was based on an exploratory *BRCA*m subgroup (n=85)**
- Patients were randomized 1:1 to receive either LYNPARZA (300 mg BID) + 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=397). 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. *BRCA*m 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 *BRCA*m subgroup analyses**
  - Investigator-assessed rPFS* and OS in patients with *BRCA*m mCRPC (n=85)
  - Sensitivity analysis of rPFS by BICR

*BRCA*m status was assessed after randomization and before primary analysis by both NGS-based tumor tissue and ctDNA tests. *BRCA*m 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.

*Radiological progression-free survival (rPFS) assessed by investigator per RECIST v1.1 (soft tissue) and PCWG3 (bone) criteria.

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

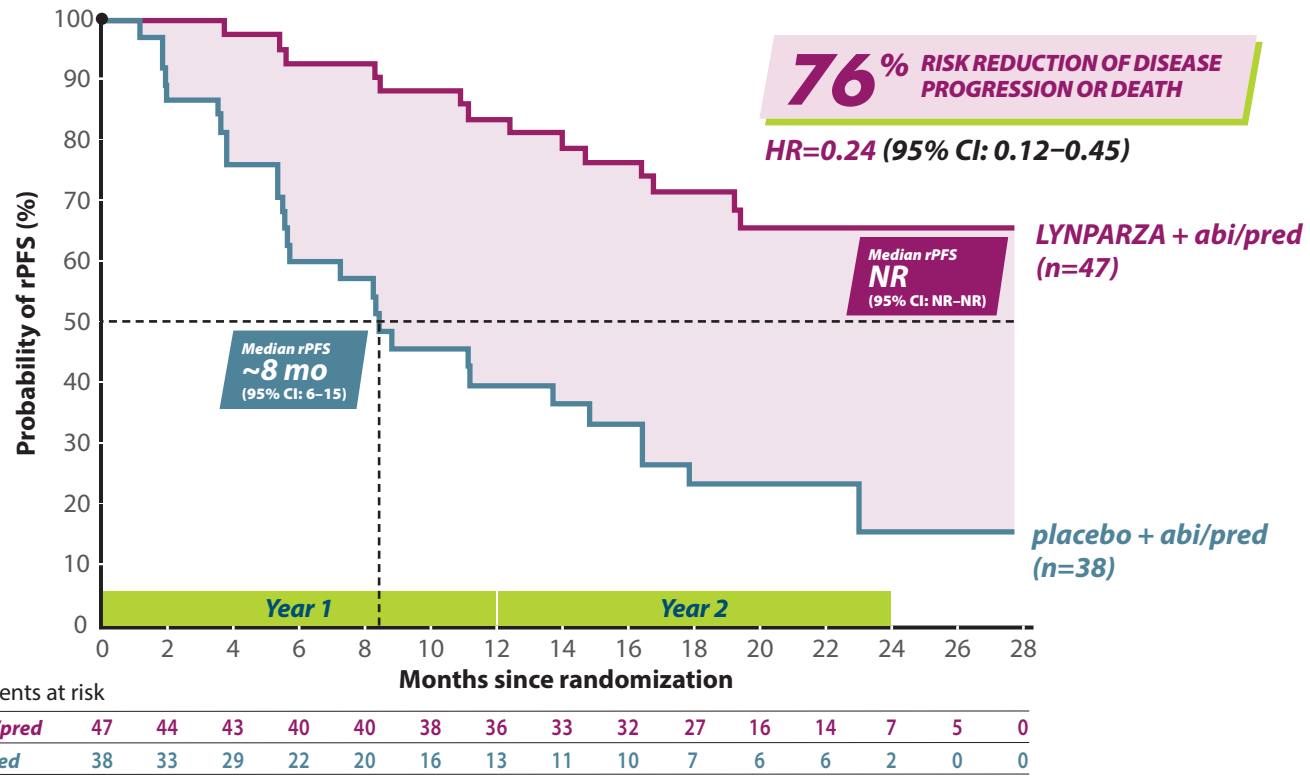
Most common adverse reactions (Grades 1-4) in ≥10% of patients who received LYNPARZA/abiraterone with a difference of ≥5% compared to placebo for **PROpel** were: anemia (48%), fatigue (including asthenia) (38%), nausea (30%), diarrhea (19%), decreased appetite (16%), lymphopenia (14%), dizziness (14%), 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 *mCRPC*[1,5]

rPFS BY INVESTIGATOR ASSESSMENT IN EXPLORATORY *BRCA*m SUBGROUP



Number of patients at risk

LYNPARZA + abi/pred	47	44	43	40	40	38	36	33	32	27	16	14	7	5	0
placebo + abi/pred	38	33	29	22	20	16	13	11	10	7	6	6	2	0	0

***BRCA*m 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

*BRCA*m 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 *BRCA*m (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 *BRCA*m 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 (CLcr 51-80 mL/min estimated by Cockcroft-Gault). In patients with moderate renal impairment (CLcr 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 (CLcr ≤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.

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

References: 1. LYNPARZA® (olaparib) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2023. **2.** Rubraca® (rucaparib) [prescribing information]. Boulder, CO: Clovis Oncology, Inc.; 2022. **3.** Talzenna® (talazoparib) [prescribing information]. New York, NY: Pfizer Inc.; 2021. **4.** Zejula® (niraparib) [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; 2023. **5.** Clarke NW, Armstrong AJ, Thiery-Vuillemin A, et al. Abiraterone and olaparib for metastatic castration-resistant prostate cancer. *NEJM Evid*. Published online June 3, 2022. doi:10.1056/EVIDoa2200043

abi/pred=abiraterone plus prednisone or prednisolone; BICR=blinded independent central review; BID=twice daily; *BRCA*m=*BRCA*-mutated or *BRCA* mutation; CI=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; mHSPC=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.

LYNPARZAprhcp.com to explore additional data from the PROpel trial

MERCK AstraZeneca

LYNPARZA® (olaparib) tablets, for oral use

Initial U.S. Approval: 2014

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza *[see Dosage and Administration (2.1) in the full Prescribing Information]*.

Treatment of *BRCA*-mutated Metastatic Castration-Resistant Prostate Cancer in Combination with Abiraterone and Prednisone or Prednisolone

Lynparza is indicated in combination with abiraterone and prednisone or prednisolone 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 *[see Dosage and Administration (2.1) in the full Prescribing Information]*.

DOSAGE AND ADMINISTRATION

Patient Selection

Information on FDA-approved tests for the detection of genetic mutations is available at http://www.fda.gov/companiondiagnostics.

Select patients for treatment with Lynparza based on the presence of deleterious or suspected deleterious HRR gene mutations, including *BRCA* mutations, or genomic instability based on the indication, biomarker, and sample type (Table 1).

Table 1 Biomarker Testing for Patient Selection*

Indication	Biomarker	Sample type		
		Tumor	Blood	Plasma (ctDNA)
Germline or somatic HRR gene-mutated metastatic castration-resistant prostate cancer	*ATM*m, *BRCA1*m, *BRCA2*m, *BARD1*m, *BRIP1*m, *CDK12*m, *CHEK1*m, *CHEK2*m, *FANCL*m, *PALB2*m, *RAD51B*m, *RAD51C*m, *RAD51D*m, *RAD54L*m	X		
	g*BRCA1*m, g*BRCA2*m		X	
	*ATM*m, *BRCA1*m, *BRCA2*m			X
BRCA-mutated metastatic castration-resistant prostate cancer in combination with abiraterone and prednisone or prednisolone	*BRCA1*m, *BRCA2*m	X	X	X

* Where testing fails or tissue sample is unavailable/insufficient, or when germline testing is negative, consider using an alternative test, if available.

Recommended Dosage

The recommended dosage of Lynparza is 300 mg taken orally twice daily, with or without food.

If a patient misses a dose of Lynparza, instruct patient to take their next dose at its scheduled time. Instruct patients to swallow tablets whole. Do not chew, crush, dissolve, or divide tablet.

HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

Continue treatment until disease progression or unacceptable toxicity for:

- HRR gene-mutated metastatic castration-resistant prostate cancer

BRCA-mutated Metastatic Castration-Resistant Prostate Cancer in Combination with Abiraterone and Prednisone or Prednisolone

Continue treatment until disease progression or unacceptable toxicity.

When used with Lynparza, the recommended dose of abiraterone is 1000 mg taken orally once daily. Abiraterone should be given in combination with prednisone or prednisolone 5 mg orally twice daily. Refer to the Prescribing Information for abiraterone for dosing information.

Patients with mCRPC should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

Dosage Modifications for Adverse Reactions

To manage adverse reactions, consider interruption of treatment or dose reduction. The recommended dose reduction is 250 mg taken twice daily.

If a further dose reduction is required, then reduce to 200 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.

If concomitant use cannot be avoided, reduce Lynparza dosage to:

- 100 mg twice daily when used concomitantly with a strong CYP3A inhibitor.
- 150 mg twice daily when used concomitantly with a moderate CYP3A inhibitor.

After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the Lynparza dose taken prior to initiating the CYP3A inhibitor *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Dosage Modifications for Renal Impairment

Moderate Renal Impairment

In patients with moderate renal impairment (CLcr 31-50 mL/min), reduce the Lynparza dosage to 200 mg orally twice daily *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Myelodysplastic Syndrome/Acute Myeloid Leukemia

Myelodysplastic syndrome (MDS)/Acute Myeloid Leukemia (AML) has occurred in patients treated with Lynparza and some cases were fatal.

In clinical studies enrolling 2901 patients with various cancers who received Lynparza as a single agent *[see Adverse Reactions (6.1) in the full Prescribing Information]*, the cumulative incidence of MDS/AML was approximately 1.5% (43/2901). Of these, 51% (22/43) had a fatal outcome. The median duration of therapy with Lynparza in patients who developed MDS/AML was 2 years (range: < 6 months to > 10 years). All of these patients had received 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 counts 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. If MDS/AML is confirmed, discontinue Lynparza.

Pneumonitis

In clinical studies enrolling 2901 patients with various cancers who received Lynparza as a single agent *[see Adverse Reactions (6.1) in the full Prescribing Information]*, the incidence of pneumonitis, including fatal cases, was 0.8% (24/2901). If patients present with new or worsening respiratory symptoms such as dyspnea, cough and fever, or a radiological abnormality occurs, interrupt Lynparza treatment and promptly assess the source of the symptoms. If pneumonitis is confirmed, discontinue Lynparza treatment and treat the patient appropriately.

Venous Thromboembolism

Venous thromboembolism (VTE), including severe or fatal pulmonary embolism (PE), occurred in patients treated with Lynparza *[see Adverse Reactions (6.1) in the full Prescribing Information]*.

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 clinical 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

Lynparza can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. In an animal reproduction study, 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. Apprise pregnant women of the potential hazard to a fetus and the potential risk for loss of the pregnancy. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Lynparza. Based on findings from 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 *[see Use in Specific Populations (8.1, 8.3) in the full Prescribing Information]*.

ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Myelodysplastic Syndrome/Acute Myeloid Leukemia *[see Warnings and Precautions (5.1) in the full Prescribing Information]*
- Pneumonitis *[see Warnings and Precautions (5.2) in the full Prescribing Information]*
- Venous Thromboembolism *[see Warnings and Precautions (5.3) in the full Prescribing Information]*

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Unless otherwise specified, the data described in the WARNINGS AND PRECAUTIONS reflect exposure to Lynparza as a single agent in 2901 patients; 2135 patients with exposure to 300 mg twice daily tablet dose including five controlled, randomized, trials (SOLO-1, SOLO-2, OlympiAD, POLO, and PROfound) and to 400 mg twice daily capsule dose in 766 patients in other trials that were pooled to conduct safety analyses. In addition to the 2901 patients, certain subsections in the WARNINGS AND PRECAUTIONS include adverse reactions observed with exposure to Lynparza with abiraterone (n=398) in PROpel. All patients with metastatic castration resistant prostate cancer received concomitant ADT or previous bilateral orchiectomy.

In the pooled safety population, 56% of patients were exposed for 6 months or longer and 28% were exposed for greater than one year in the Lynparza group.

In this pooled safety population, the most common adverse reactions in ≥10% of patients were nausea (60%), fatigue (55%), anemia (36%), vomiting (32%), diarrhea (24%), decreased appetite (22%), headache (16%), dysgeusia (15%), cough (15%), neutropenia (14%), dyspnea (14%), dizziness (12%), dyspepsia (12%), leukopenia (11%), and thrombocytopenia (10%).

HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

PROfound

The safety of Lynparza as monotherapy was evaluated in patients with mCRPC and HRR gene mutations who have progressed following prior treatment with enzalutamide or abiraterone in PROfound *[see Clinical Studies (14.7) in the full Prescribing Information]*. This study was a randomized, open-label, multi-center study in which 386 patients received either Lynparza tablets 300 mg orally twice daily (n=256) or investigator's choice of enzalutamide or abiraterone acetate (n=130) until disease progression or unacceptable toxicity. Among patients receiving Lynparza, 62% were exposed for 6 months or longer and 20% were exposed for greater than one year.

Fatal adverse reactions occurred in 4% of patients treated with Lynparza. These included pneumonia (1.2%), cardiopulmonary failure (0.4%), aspiration pneumonia (0.4%), intestinal diverticulum (0.4%), septic shock (0.4%), Budd-Chiari Syndrome (0.4%), sudden death (0.4%), and acute cardiac failure (0.4%).

Serious adverse reactions occurred in 36% of patients receiving Lynparza. The most frequent serious adverse reactions (≥2%) were anemia (9%), pneumonia (4%), pulmonary embolism (2%), fatigue/asthenia (2%), and urinary tract infection (2%).

Dose interruptions due to an adverse reaction of any grade occurred in 45% of patients receiving Lynparza; dose reductions due to an adverse reaction occurred in 22% of Lynparza patients. The most frequent adverse reactions leading to dose interruption of Lynparza were anemia (25%) and thrombocytopenia (6%) and the most frequent adverse reaction leading to reduction of Lynparza was anemia (16%). Discontinuation due to adverse reactions occurred in 18% of Lynparza. The adverse reaction that most frequently led to discontinuation of Lynparza was anemia (7%).

Tables 16 and 17 summarize the adverse reactions and laboratory abnormalities, respectively, in patients in PROfound.

Table 16 Adverse Reactions* Reported in ≥10% of Patients in PROfound

Adverse Reactions	Lynparza tablets n=256		Enzalutamide or abiraterone n=130	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Blood and lymphatic disorders				
Anemia†	46	21	15	5
Thrombocytopenia‡	12	4	3	0
Gastrointestinal disorders				
Nausea	41	1	19	0
Diarrhea	21	1	7	0
Vomiting	18	2	12	1
General disorders and administration site conditions				
Fatigue (including asthenia)	41	3	32	5
Metabolism and nutrition disorders				
Decreased appetite	30	1	18	1
Respiratory, thoracic, and mediastinal disorders				
Cough	11	0	2	0
Dyspnea	10	2	3	0

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.
† Includes anemia and hemoglobin decreased.
‡ Includes platelet count decreased and thrombocytopenia.

Clinically relevant adverse reactions that occurred in <10% of patients receiving Lynparza were neutropenia (9%), VTE (7%), dizziness (7%), dysgeusia (7%), dyspepsia (7%), headache (6%), pneumonia (5%), stomatitis (5%), rash (4%), blood creatinine increase (4%), pneumonitis (2%), upper abdominal pain (2%), and hypersensitivity (1%).

Table 17 Laboratory Abnormalities Reported in ≥25% of Patients in PROfound

Laboratory Parameter*	Lynparza tablets n†= 256		Enzalutamide or abiraterone n†=130	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in hemoglobin	98	13	73	4
Decrease in lymphocytes	62	23	34	13
Decrease in leukocytes	53	4	21	0
Decrease in absolute neutrophil count	34	3	9	0

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.
† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

Treatment of *BRCA*-mutated Metastatic Castration-Resistant Prostate Cancer in Combination with Abiraterone and Prednisone or Prednisolone

PROpel

The safety of Lynparza in combination with abiraterone and prednisone or prednisolone for the treatment of patients in the first-line mCRPC setting was investigated in PROpel *[see Clinical Studies (14.8) in the full Prescribing Information]*. Patients were randomized to receive either Lynparza tablets 300 mg orally twice daily plus abiraterone tablets 1000 mg once daily (Lynparza/abiraterone) (n=398), or placebo plus abiraterone 1000 mg once daily (placebo/abiraterone) (n=396) until disease progression or unacceptable toxicity. Patients in both arms also received either prednisone or prednisolone 5 mg twice daily.

Fatal adverse reactions occurred in 6% of patients, including COVID-19 (3%) and pneumonias (0.5%).

Serious adverse reactions occurred in 39% of patients. Serious adverse reactions reported in > 2% of patients included anemia (6%), COVID-19 (6%), pneumonia (4.5%), pulmonary embolism (3.5%), and urinary tract infection (3%).

Permanent discontinuation of Lynparza due to adverse reactions occurred in 16% of patients treated in the Lynparza with abiraterone arm. The most common adverse reactions which resulted in permanent discontinuation of Lynparza were anemia (4.3%) and pneumonia (1.5%).

Dosage interruption of Lynparza due to adverse reactions occurred in 48% of patients treated in the Lynparza with abiraterone arm. The most common (>2%) adverse reactions requiring dosage interruption of Lynparza were anemia (16%), COVID-19 (6%) fatigue (3.5%), nausea (2.8%), pulmonary embolism (2.3%), and diarrhea (2.3%).

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 (2.5%).

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 dizziness (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

Adverse Reactions*	Lynparza/abiraterone n=398		Placebo/abiraterone n=396	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Blood and Lymphatic Disorders				
Anemia†	48	16	18	3.3
Lymphopenia‡	14	5	6	1.8
General Disorders and Administration Site Conditions				
Fatigue (including asthenia)	38	2.3	30	1.5
Gastrointestinal Disorders				
Nausea	30	0.3	14	0.3
Diarrhea	19	1	10	0.3
Abdominal pain$^{\alpha}$	13	0	7	0.5
Metabolism and nutrition disorders				
Decreased appetite	16	1	7	0
Nervous System Disorders				
Dizziness$^{\beta}$	14	0.3	7	0

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.
† Includes anemia, anemia macrocytic, and red blood cell count decreased
‡ Includes lymphocyte count decreased and lymphopenia
$^{\alpha}$ Includes abdominal discomfort, abdominal pain, abdominal pain upper, and abdominal pain lower
$^{\beta}$ Includes dizziness and vertigo.

Clinically relevant adverse reactions that occurred in <10% for patients receiving Lynparza plus abiraterone were headache (9%), VTE (8%), rash (7%), dysgeusia (6%), acute kidney injury (3%), and stomatitis (2.5%).

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

Laboratory Parameter	Lynparza/abiraterone n=398†		Placebo/abiraterone n=396†	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in hemoglobin	97	12	81	1.3
Decrease in lymphocytes	70	23	49	11
Decrease in platelets	23	1.2	20	0.3
Decrease in absolute neutrophil count	23	5	6	0

† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

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.

Skin and subcutaneous tissue disorders: Erythema nodosum, rash, dermatitis.

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

Strong and Moderate CYP3A Inhibitors

Coadministration 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 coadministration of strong or moderate CYP3A inhibitors. If the strong or moderate inhibitor must be coadministered, reduce the dose of Lynparza *[see Dosage and Administration (2.4) in the full Prescribing Information]*.

Strong and Moderate CYP3A Inducers

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 coadministration of strong or moderate CYP3A inducers.

USE IN SPECIFIC POPULATIONS

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 for spontaneous abortion is approximately 15-20% in clinically recognized pregnancies.

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 ($AUC_{0\text{-}24h}$) 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 ($AUC_{0\text{-}24h}$) at the recommended dose) caused embryo-fetal toxicities including increased post-implantation loss and major malformations of the eyes (anophthalmia, microphthalmia), vertebrae/ribs (extra rib or ossification center; fused or absent neural arches, ribs, and sternebrae), skull (fused exoccipital), and diaphragm (hernia). Additional abnormalities or variants included incomplete or absent ossification (vertebrae/sternebrae, ribs, limbs) and other findings in the vertebrae/sternebrae, pelvic girdle, lung, thymus, liver, ureter, and umbilical artery. Some findings noted above in the eyes, ribs, and ureter were observed at a dose of 0.05 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 after receiving 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

Of the 2901 patients with advanced solid tumors who received Lynparza as a single agent, 680 (23%) patients were aged ≥65 years, and this included 206 (7%) patients who were aged ≥75 years. Thirteen (0.4%) patients were aged ≥85 years.

Of the 535 patients with advanced solid tumors who received Lynparza tablets 300 mg orally twice daily in combination with bevacizumab (PAOLA-1), 204 (38%) patients were aged ≥65 years, and this included 31 (6%) patients who were aged ≥75 years.

Of the 398 patients with advanced solid tumors who received Lynparza tablets 300 mg orally twice daily in combination with abiraterone and prednisone or prednisolone (PROpel), 268 (67%) patients were aged ≥65 years, and this included 95 (24%) patients who were aged ≥75 years.

No overall differences in the safety or 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 51 to 80 mL/min estimated by Cockcroft-Gault). Reduce Lynparza dosage to 200 mg twice daily in patients with moderate renal impairment (CLcr 31 to 50 mL/min) *[see Dosage and Administration (2.5) in the full Prescribing Information]*. There are no data 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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05/23 US-63563 6/23

AUA TAKE 5

THE TOP 5 AUA HAPPENINGS THIS MONTH!

1

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AUAnet.org/2024Abstracts

2

Don't miss the 2-part *AUANews*Worthy Webinar about the AUA/Society of Urologic Oncology Guideline, "Diagnosis and Management of Non-Metastatic Upper Tract Urothelial Carcinoma (UTUC)." This guideline provides a useful reference on the effective evidence-based diagnoses and management of nonmetastatic UTUC. Drs Jonathan Coleman, Phil Pierorazio, and Sarah Psutka, all panel members for the Guideline, share their time for 2 in-depth conversations about this guideline.

AUANews.net/UTUC

3

Take the Census to Win! Members completing the Census online by September 30, 2023, will be offered the opportunity to enter a drawing to win an electronic gift card ranging in value from $50 to $100. Only 1 entry per person is permitted.

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4

Learn How to Move Your Urological Idea From Concept to Realization at the AUA Innovation Nexus Boot Camp! This 2-day workshop prepares and empowers attendees to take their innovative ideas and develop them into a marketable product. Hear from successful inventors, participate in intimate roundtable discussions, and network with others on an individual level.

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5

New Release: 2024 Self-Assessment Study Program (SASP) Available to Pre-order! With over 3.2 million questions answered, the AUA's SASP is our most popular study tool for exam preparation. The SASP app provides 150 customizable multiple choice questions on the core curriculum of urology knowledge and latest advances in patient care to help you enhance your learning. Pre-order your 2024 SASP now!

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AUANews

September 2023, Volume 28 | Issue 9

PUBLICATIONS DEPARTMENT
American Urological Association
publications@AUAnet.org

PRODUCTION
KnowledgeWorks Global Ltd.
2905 Byrdhill Road, Richmond, VA 23228

ADVERTISING SALES
The Walchli Tauber Group
(443) 512-8899
stephen.tauber@wt-group.com

AUANews is the official newsmagazine of the American Urological Association, located at 1000 Corporate Blvd., Linthicum, MD 21090, and is a function of the AUA Education and Research, Inc. AUANews is published 24 times a year by the American Urological Association.

Published free of charge for AUA membership. Annual non-member subscription rates: individual $110 ($155 foreign); institution $135 ($180 foreign); industry $65 ($135 foreign). U.S. POSTMASTER: Send address changes to *AUANews*, American Urological Association, 1000 Corporate Blvd., Linthicum, MD 21090. Library of Congress ISSN: 1088-7350. All correspondence on editorial matters should be addressed to: Executive Editor, American Urological Association, 1000 Corporate Boulevard, Linthicum, MD 21090.

PROSTATE CANCER

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).

> "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."

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 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.

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

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

REACHING FOR HEALTH EQUITY IN PROSTATE CANCER CARE THROUGH ADVOCACY

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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.[4] 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.[5] 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.[6,7] 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.[8] 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.[8]

> "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."

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. ■

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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.[1-3] 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 heterogenous 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).[1] To understand the molecular differences between peripheral zone (PZ) and

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NOVEL MOLECULAR PROFILING TECHNOLOGY APPLICATIONS

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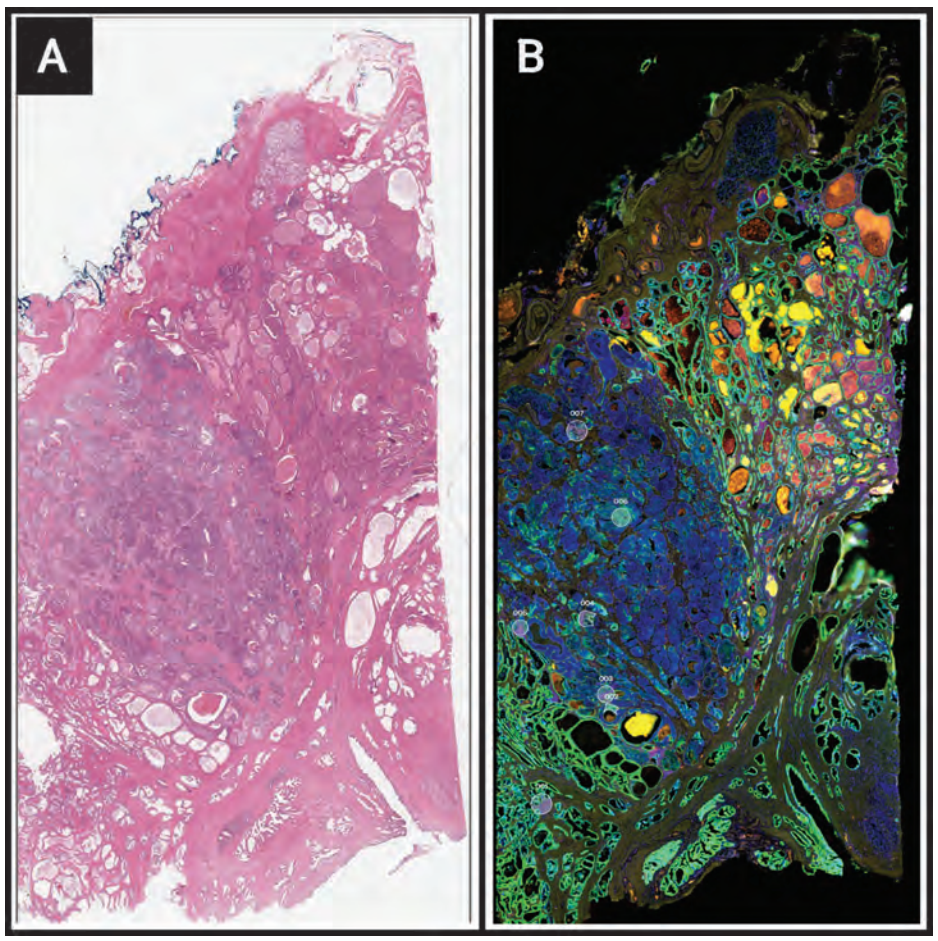

Figure. A, Hematoxylin and eosin (H&E) image of radical prostatectomy specimen displaying prostate cancer in the peripheral zone. B, Immunofluorescence (IF) image using morphology markers to delineate the nucleus (SYTO13—blue), epithelium (PanCK—green), stroma/smooth muscle (SMA/ACTA2—yellow), and immune 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.

transition zone (TZ) prostate cancers, our group utilized DSP to analyze tumor samples obtained from 3 patients who underwent radical prostatectomy for prostate cancer. We analyzed 50 ROIs from PZ and TZ with a total capture of 17,128 genes. Differential gene expression and pathway enrichment analyses revealed that androgen response signaling was upregulated in TZ tumors compared to PZ tumors. With the capacity of the DSP to segment ROI into areas of interest, we localized the enrichment of androgen response signaling to the epithelium. Taken together, these findings provide insights into the biologic differences between PZ and TZ prostate cancers.

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 orchiectomy in association with changes in the tissue architecture. We orchiectomized 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 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.[1-2] 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.[4] 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 Drop-seq 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.[4-6] 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

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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. ■

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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 perivesical 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 (oLC) 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%

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PERITONEAL INTERPOSITION FLAPS SUBSEQUENT TO ROBOT-ASSISTED RADICAL PROSTATECTOMY

→ Continued from page 10

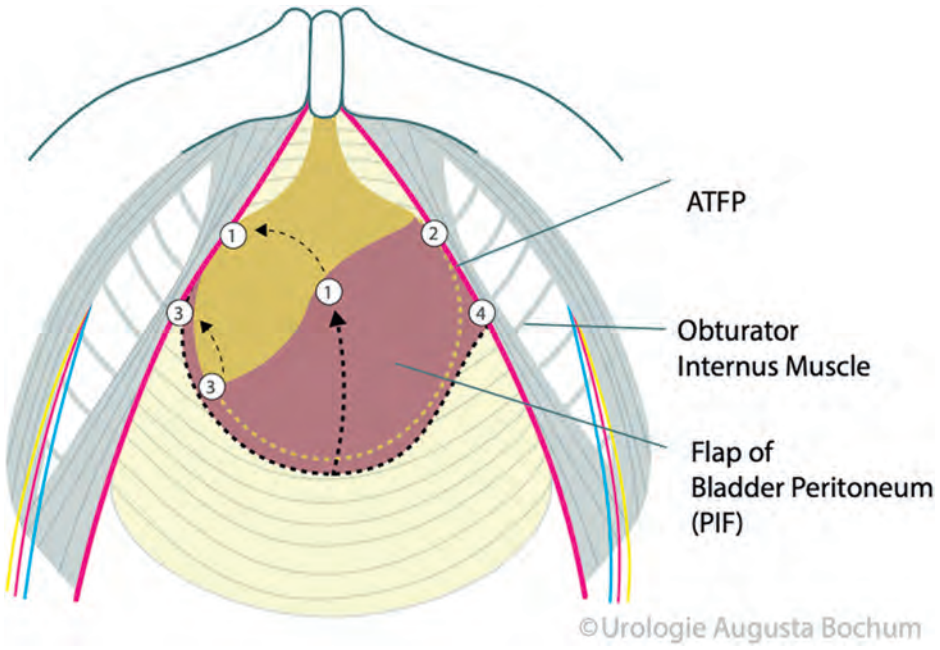

Figure. To create bilateral peritoneal flaps, the edges of the bladder peritoneum are sutured to the endopelvis, here demonstrated for the endopelvic fascia, as it was performed in the ProLy study. The illustration shows the completed procedure on the right side. ATFP indicates arcus tendineus fasciae pelvis; PIF, peritoneal interposition flap.

($P = .03$).[9] 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, 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.[10] 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 periost of the pubic bone.

The US single-center, single-surgeon PLUS study included a total of 216 men.[11] 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 Pianoforte study contrast with the studies already mentioned.[12] 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,[13] 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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NUBEQA®
(darolutamide) 300 mg tablets

FOR YOUR PATIENTS WITH **mHSPC** OR **nmCRPC**

HELP HIM LIVE FOR WHAT HE LOVES

NUBEQA REDUCED THE RISK OF DEATH BY >30% ACROSS mHSPC and nmCRPC[1-5]

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/m^2 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, ^{99m}Tc 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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INDICATIONS

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

- Non-metastatic castration-resistant prostate cancer (nmCRPC)
- Metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel

IMPORTANT SAFETY INFORMATION

Warnings & Precautions

Ischemic Heart Disease – In a study of patients with nmCRPC (ARAMIS), ischemic heart disease occurred in 3.2% of patients receiving NUBEQA versus 2.5% receiving placebo, including Grade 3-4 events in 1.7% vs. 0.4%, respectively. Ischemic events led to death in 0.3% of patients receiving NUBEQA vs. 0.2% receiving placebo. In a study of patients with mHSPC (ARASENS), ischemic heart disease occurred in 2.9% of patients receiving NUBEQA with docetaxel vs. 2% receiving placebo with docetaxel, including Grade 3-4 events in 1.3% vs. 1.1%, respectively. Ischemic events led to death in 0.3% of patients receiving NUBEQA with docetaxel vs. 0% receiving placebo with docetaxel. Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue NUBEQA for Grade 3-4 ischemic heart disease.

Seizure – In ARAMIS, Grade 1-2 seizure occurred in 0.2% of patients receiving NUBEQA vs. 0.2% receiving placebo. Seizure occurred 261 and 456 days after initiation of NUBEQA. In ARASENS, seizure occurred in 0.6% of patients receiving NUBEQA with docetaxel, including one Grade 3 event, vs. 0.2% receiving placebo with docetaxel. Seizure occurred 38 to 340 days after initiation of NUBEQA. It is unknown whether anti-epileptic medications will prevent seizures with NUBEQA. Advise patients of the risk of developing a seizure while receiving NUBEQA and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others. Consider discontinuation of NUBEQA in patients who develop a seizure during treatment.

Embryo-Fetal Toxicity – Safety and efficacy of NUBEQA have not been established in females. NUBEQA can cause fetal harm and loss of pregnancy. Advise males with female partners of reproductive potential to use effective contraception during treatment with NUBEQA and for 1 week after the last dose.

Adverse Reactions

In ARAMIS, serious adverse reactions occurred in 25% of patients receiving NUBEQA vs. 20% of patients receiving placebo. Serious adverse reactions in ≥1% of patients who received NUBEQA included urinary retention, pneumonia, and hematuria. Fatal adverse reactions occurred in 3.9% of patients receiving NUBEQA vs. 3.2% of patients receiving placebo. Fatal adverse reactions in patients who received NUBEQA included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%). The most common adverse reactions (>2% with a ≥2% increase over placebo), including laboratory test abnormalities, were increased AST, decreased neutrophil count, fatigue, increased bilirubin, pain in extremity, and rash. Clinically relevant adverse reactions occurring in ≥2% of patients treated with NUBEQA included ischemic heart disease and heart failure.

In ARASENS, 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 P-gp and strong or moderate CYP3A4 inducers decrease NUBEQA exposure, which may decrease NUBEQA activity. Avoid concomitant use.

Combined P-gp 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 orchiectmy.

References: 1. NUBEQA (darolutamide) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc.; August 2022. **2.** Smith MR, Hussain M, Saad F, et al; ARASENS Trial Investigators. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. *N Engl J Med.* 2022;386(12):1132-1142. **3.** Fizazi K, Shore N, Tammela T2, et al. Nonmetastatic, castration-resistant prostate cancer and survival with darolutamide. *N Engl J Med.* 2020;383(11):1040-1049. **4.** Fizazi K, Shore N, Tammela TL, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med.* 2019;380(13):1235-1246.

Please see the following page(s) for the brief summary of Prescribing Information.

PP-NUB-US-2624-1 07/23

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NUBEQA® (darolutamide) tablets, for oral use
Initial U.S. Approval: 2019

BRIEF SUMMARY OF PRESCRIBING INFORMATION
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE NUBEQA is indicated for the treatment of adult patients with:
- non-metastatic castration resistant prostate cancer (nmCRPC)
- metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel.

4 CONTRAINDICATIONS None.

5 WARNINGS AND PRECAUTIONS

5.1 Ischemic Heart Disease Ischemic heart disease, including fatal cases, occurred in patients receiving NUBEQA.
In a randomized study of patients with nmCRPC (ARAMIS), ischemic heart disease occurred in 3.2% of patients receiving NUBEQA and 2.5% receiving placebo, including Grade 3-4 events in 1.7% and 0.4%, respectively. Ischemic events led to death in 0.3% of patients receiving NUBEQA and 0.2% receiving placebo.
In a randomized study of patients with mHSPC (ARASENS), ischemic heart disease occurred in 2.9% of patients receiving NUBEQA with docetaxel and 2% receiving placebo with docetaxel, including Grade 3-4 events in 1.3% and 1.1%, respectively. Ischemic events led to death in 0.3% of patients receiving NUBEQA with docetaxel and 0% receiving placebo with docetaxel.
Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue NUBEQA for Grade 3-4 ischemic heart disease.

5.2 Seizure Seizure occurred in patients receiving NUBEQA.
In ARAMIS, Grade 1-2 seizure occurred in 0.2% of patients receiving NUBEQA and 0.2% receiving placebo. Seizure occurred 261 and 456 days after initiation of NUBEQA.
In ARASENS, seizure occurred in 0.6% of patients receiving NUBEQA with docetaxel, including one Grade 3 event, and 0.2% receiving placebo with docetaxel. Seizure occurred 38 to 340 days after initiation of NUBEQA.
It is unknown whether anti-epileptic medications will prevent seizures with NUBEQA. Advise patients of the risk of developing a seizure while receiving NUBEQA and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others. Consider discontinuation of NUBEQA in patients who develop a seizure during treatment.

5.3 Embryo-Fetal Toxicity The safety and efficacy of NUBEQA have not been established in females. Based on its mechanism of action, NUBEQA can cause fetal harm and loss of pregnancy when administered to a pregnant female *[see Clinical Pharmacology]*.
Advise males with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA *[see Use in Specific Populations]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
Non-Metastatic Castration Resistant Prostate Cancer The safety of NUBEQA was evaluated in ARAMIS, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, that enrolled patients who had non-metastatic castration-resistant prostate cancer (nmCRPC) *[see Clinical Studies]*. Patients received either NUBEQA at a dose of 600 mg, or a placebo, twice a day. All patients in the ARAMIS study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. Among patients who received NUBEQA, the median duration of exposure was 14.8 months (range: 0 to 44.3 months).
Serious adverse reactions occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions in ≥1% of patients who received NUBEQA included urinary retention, pneumonia and hematuria. Fatal adverse reactions occurred in 3.9% of patients receiving NUBEQA and 3.2% of patients receiving placebo. Fatal adverse reactions in patients who received NUBEQA included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%).
Permanent discontinuation of NUBEQA due to adverse reactions occurred in 9% of patients receiving NUBEQA. The most common adverse reactions requiring permanent discontinuation in patients who received NUBEQA included cardiac failure (0.4%), and death (0.4%).
Dosage interruptions due to adverse reactions occurred in 13% of patients treated with NUBEQA. The most common adverse reactions requiring dosage interruption in patients who received NUBEQA included hypertension (0.6%), diarrhea (0.5%), and pneumonia (0.5%).
Dosage reductions due to adverse reactions occurred in 6% of patients treated with NUBEQA. The most common adverse reactions requiring dosage reduction in patients treated with NUBEQA included fatigue (0.7%), hypertension (0.3%), and nausea (0.3%).
The most common (>2% with a ≥2% increase compared to placebo) adverse reactions, including laboratory test abnormalities, were AST increased, neutrophil count decreased, fatigue, bilirubin increased, pain in extremity, and rash.
Table 1 summarizes the adverse reactions in ARAMIS.

Table 1: Adverse Reactions (>2% with a ≥2% increase compared to placebo) in Patients with Non-Metastatic Castration Resistant Prostate Cancer in ARAMIS

Adverse Reaction	NUBEQA (n=954)		Placebo (n=554)	
	All Grades %	Grades 3 or 4 %	All Grades %	Grade 3 or 4 %
Fatigue[1]	16	0.6	11	1.1
Pain in extremity	6	0	3	0.2
Rash[2]	4	0.1	1.4	0

[1] Includes fatigue and asthenia
[2] Includes rash, eczema, rash maculo-papular, dermatitis, erythema multiforme, rash macular, rash papular, rash pustular, skin exfoliation

Clinically relevant adverse reactions occurring in 2% or more of patients treated with NUBEQA included ischemic heart disease (4%) and heart failure (2.1%).
Table 2 summarizes the laboratory test abnormalities in ARAMIS.

Table 2: Laboratory Test Abnormalities in ARAMIS

Laboratory Abnormality	NUBEQA (N=954)[1]		Placebo (N=554)[1]	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
AST increased	23	0.5	14	0.2
Neutrophil count decreased	20	4	9	0.6
Bilirubin increased	16	0.1	7	0

[1] The denominator used to calculate the rate varied based on the number of patients with a baseline value and at least one post-treatment value.

Metastatic Hormone-Sensitive Prostate Cancer The safety of NUBEQA, in combination with docetaxel, was evaluated in ARASENS, a randomized (1:1), double-blind, placebo-controlled, multi-center clinical study, that enrolled patients who had mHSPC *[see Clinical Studies]*. Patients were to receive either NUBEQA at a dose of 600 mg, or a placebo, twice a day in combination with docetaxel at a dose of 75 mg/m2 every 21 days for 6 cycles. All patients in the ARASENS study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. Patients with a medical history of seizure were allowed to enter the study. Among patients who received NUBEQA, the median duration of exposure was 41 months (range: 0.1 to 56.5 months) vs. 16.7 months (range 0.3 to 55.8) with placebo. Eighty-eight percent and 86% of patients received the 6 planned cycles of docetaxel, in the NUBEQA with docetaxel arm and placebo with docetaxel arm, respectively.
Serious adverse reactions occurred in 45% of patients receiving NUBEQA with docetaxel and in 42% of patients receiving placebo with docetaxel, respectively. Serious adverse reactions in ≥ 2% of patients who received NUBEQA with docetaxel included febrile neutropenia (6%), neutrophil count decreased (2.8%), musculoskeletal pain (2.6%) and pneumonia (2.6%). Fatal adverse reactions occurred in 4% of patients receiving NUBEQA with docetaxel and 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%).
Permanent discontinuation of NUBEQA due to adverse reactions occurred in 14% of patients treated in the NUBEQA with docetaxel arm. The most common adverse reactions which resulted in permanent discontinuation of NUBEQA were rash (1.1%), musculoskeletal pain (0.9%), and aspartate aminotransferase (AST) increased (0.9%).
Dosage interruptions of NUBEQA due to adverse reactions occurred in 23% of patients treated in the NUBEQA with docetaxel arm. The most common (>2%) adverse reactions requiring dosage interruption of NUBEQA were alanine aminotransferase (ALT) increased (3.2%), AST increased (3.1%) and febrile neutropenia (2.1%).
Dosage reductions of NUBEQA due to adverse reactions occurred in 9% of patients treated in the NUBEQA with docetaxel arm. The most common (>2%) adverse reactions requiring dosage reduction of NUBEQA were ALT increased (2.8%) and AST increased (2.5%).
The most common (>10% with a ≥2% increase over placebo with docetaxel) adverse reactions are constipation, decreased appetite, rash, hemorrhage, weight increased, and hypertension. The most common laboratory test abnormalities (≥30%) are anemia, hyperglycemia, lymphocyte count decreased, neutrophil count decreased, AST increased, ALT increased, and hypocalcemia.
Table 3 summarizes the adverse reactions in ARASENS.

Table 3: Adverse Reactions (≥10% with a ≥2% increase compared to placebo with docetaxel) in ARASENS

Adverse Reaction	NUBEQA with docetaxel (n=652)		Placebo with docetaxel (n=650)	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Constipation	23	0.3	20	0.3
Decreased Appetite	19	0.2	13	0.6
Rash[1]	19	1.8	15	0.2
Hemorrhage[2]	18	1.4	13	1.4
Weight Increased	18	2.1	16	1.2
Hypertension[3]	14	7	9	3.7

[1] Rash includes rash, rash maculo-papular, palmar-plantar erythrodysesthesia syndrome, eczema, dermatitis, skin exfoliation, dermatitis acneiform, drug eruption, rash pruritic, rash erythematous, erythema multiforme, rash macular, dermatitis exfoliative generalized, penile rash, dyshidrotic eczema, rash papular, dermatitis bullous, rash follicular, rash pustular, rash vesicular, toxic skin eruption
[2] Hemorrhage includes hematuria, epistaxis, anal hemorrhage, hemorrhoidal hemorrhage, rectal hemorrhage, upper gastrointestinal hemorrhage, hemoptysis, hemorrhage urinary tract, hemorrhagic stroke, subarachnoid hemorrhage, lower gastrointestinal hemorrhage, cystitis hemorrhagic, gastrointestinal hemorrhage, hemorrhage subcutaneous, intra-abdominal hemorrhage, nail bed bleeding, subdural hemorrhage
[3] Hypertension includes hypertension, blood pressure increased, hypertensive emergency and hypertensive crisis.

Clinically relevant adverse reactions in < 10% of patients who received NUBEQA with docetaxel included fractures (8%), ischemic heart disease (2.9%), seizures (0.6%), and drug-induced liver injury (0.3%).
Table 4 summarizes laboratory test abnormalities in the ARASENS study.

Table 4: Laboratory Test Abnormalities (≥30%) in ARASENS

Laboratory Abnormality	NUBEQA with docetaxel[1] (N=652)		Placebo with docetaxel[1] (N=650)	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Anemia	72	6	71	7
Hyperglycemia	57	7	53	10
Lymphocyte count decreased	52	12	49	13
Neutrophil count decreased	49	33	44	31
AST increased[2]	40	3.6	35	2.3
ALT increased[2]	37	3.7	31	2.9
Hypocalcemia	31	2.8	28	1.9

[1] The denominator used to calculate the rate varied from 470 to 648 based on the number of patients with a baseline value and at least one post-treatment value.
[2] ALT or AST increases to ≥5 x upper limit of normal (ULN) occurred in 5.3% of patients who received NUBEQA with docetaxel. ALT or AST increases to ≥20 x ULN occurred in 0.3% of patients who received NUBEQA with docetaxel. The median time to onset of any grade ALT or AST increases was 2.8 months (range: 0.03 to 46.9).

Clinically relevant laboratory test abnormalities in < 30% of patients who received NUBEQA with docetaxel included blood bilirubin increased (all grades 20%, Grade 3-4 0.5%) compared to placebo with docetaxel (all grades 10%, grades 3-4 0.3%).

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on NUBEQA
Combined P-gp and Strong or Moderate CYP3A4 Inducer Concomitant use of NUBEQA with a combined P-gp and strong or moderate CYP3A4 inducer decreases darolutamide exposure which may decrease NUBEQA activity *[see Clinical Pharmacology]*. Avoid concomitant use of NUBEQA with combined P-gp and strong or moderate CYP3A4 inducers.
Combined P-gp and Strong CYP3A4 Inhibitors Concomitant use of NUBEQA with a combined P-gp and strong CYP3A4 inhibitor increases darolutamide exposure *[see Clinical Pharmacology]* which may increase the risk of NUBEQA adverse reactions. Monitor patients more frequently for NUBEQA adverse reactions and modify NUBEQA dosage as needed *[see Dosage and Administration]*.

7.2 Effects of NUBEQA on Other Drugs
Breast Cancer Resistance Protein (BCRP) and Organic Anion Transporting Polypeptides (OATP) 1B1 and 1B3 Substrates
NUBEQA is an inhibitor of BCRP transporter. Concomitant use of NUBEQA increases the AUC and C_{max} of BCRP substrates *[see Clinical Pharmacology]*, which may increase the risk of BCRP substrate-related toxicities.
Avoid concomitant use with drugs that are BCRP substrates where possible. If used together, monitor patients more frequently for adverse reactions, and consider dose reduction of the BCRP substrate drug.
NUBEQA is an inhibitor of OATP1B1 and OATP1B3 transporters. Concomitant use of NUBEQA may increase the plasma concentrations of OATP1B1 or OATP1B3 substrates. Monitor patients more frequently for adverse reactions of these drugs and consider dose reduction while patients are taking NUBEQA *[see Clinical Pharmacology]*.
Review the prescribing information of the BCRP, OATP1B1 and OATP1B3 substrates when used concomitantly with NUBEQA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary The safety and efficacy of NUBEQA have not been established in females. Based on its mechanism of action, NUBEQA can cause fetal harm and loss of pregnancy *[see Clinical Pharmacology]*. Animal embryo-fetal developmental toxicology studies were not conducted with darolutamide. There are no human data on the use of NUBEQA in pregnant females.

8.2 Lactation
Risk Summary The safety and efficacy of NUBEQA have not been established in females. There are no data on the presence of darolutamide or its metabolites in human milk, the effect on the breastfed child, or the effect on milk production.

8.3 Females and Males of Reproductive Potential
Contraception *Males* Based on the mechanism of action, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA *[see Use in Specific Populations]*.
Infertility *Males* Based on animal studies, NUBEQA may impair fertility in males of reproductive potential *[see Nonclinical Toxicology]*.

8.4 Pediatric Use Safety and effectiveness of NUBEQA in pediatric patients have not been established.

8.5 Geriatric Use Of the 954 patients who received NUBEQA in ARAMIS, 88% of patients were 65 years and over, and 49% were 75 years and over. Of the 652 patients who received NUBEQA in ARASENS, 63% of patients were 65 years and over, and 16% were 75 years and over. No overall differences in safety or efficacy were observed between these patients and younger patients in both studies.

8.6 Renal Impairment Patients with severe renal impairment (eGFR 15–29 mL/min/1.73 m^2) who are not receiving hemodialysis have a higher exposure to NUBEQA and reduction of the dose is recommended *[see Dosage and Administration and Clinical Pharmacology]*. No dose reduction is needed for patients with mild or moderate renal impairment (eGFR 30-89 mL/min/1.73 m^2). The effect of end stage renal disease (eGFR ≤15 mL/min/1.73 m^2) on darolutamide pharmacokinetics is unknown.

8.7 Hepatic Impairment Patients with moderate hepatic impairment (Child-Pugh Class B) have a higher exposure to NUBEQA and reduction of the dose is recommended *[see Dosage and Administration and Clinical Pharmacology]*. No dose reduction is needed for patients with mild hepatic impairment. The effect of severe hepatic impairment (Child-Pugh C) on darolutamide pharmacokinetics is unknown.

10 OVERDOSAGE There is no known specific antidote for darolutamide overdose. The highest dose of NUBEQA studied clinically was 900 mg twice daily, equivalent to a total daily dose of 1800 mg. No dose limiting toxicities were observed with this dose.
Considering the saturable absorption and the absence of evidence for acute toxicity, an intake of a higher than recommended dose of darolutamide is not expected to lead to systemic toxicity in patients with intact hepatic and renal function *[see Clinical Pharmacology]*.
In the event of intake of a higher than recommended dose in patients with severe renal impairment or moderate hepatic impairment, if there is suspicion of toxicity, interrupt NUBEQA treatment and undertake general supportive measures until clinical toxicity has been diminished or resolved. If there is no suspicion of toxicity, NUBEQA treatment can be continued with the next dose as scheduled.

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Patient Information)
Ischemic Heart Disease Inform patients that NUBEQA has been associated with an increased risk of ischemic heart disease. Advise patients to seek immediate medical attention if any symptoms suggestive of an ischemic heart disease event occur *[see Warnings and Precautions]*.
Seizure Inform patients that NUBEQA has been associated with an increased risk of seizure. Discuss conditions that may predispose to seizures and medications that may lower the seizure threshold. Advise patients of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Inform patients to contact their healthcare provider right away if they have loss of consciousness or seizure *[see Warnings and Precautions]*.
Embryo-Fetal Toxicity Inform patients that NUBEQA can be harmful to a developing fetus and can cause loss of pregnancy *[see Use in Specific Populations]*.
Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA *[see Warnings and Precautions and Use in Specific Populations]*.
Dosage and Administration Inform patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with NUBEQA.
Instruct patients to take their dose of two tablets (twice daily). NUBEQA should be taken with food. Each tablet should be swallowed whole.
Inform patients that in the event of a missed daily dose of NUBEQA, to take any missed dose, as soon as they remember prior to the next scheduled dose, and not to take two doses together to make up for a missed dose *[see Dosage and Administration]*.
Infertility Advise male patients that NUBEQA may impair fertility *[see Use in Specific Populations]*.

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PROSTATE CANCER

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 TRBx 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

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

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

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.
[a]Start dates are listed in chronological order.
[b]Clinically significant prostate cancer is defined as Gleason score ≥7 or grade group ≥2.

RANDOMIZED CONTROLLED TRIALS TO INFORM PROSTATE BIOPSY DEBATE

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> "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."

favoring TP-Bx, a number of barriers to the adoption of TP-Bx have been identified.[16] TP-Bx is associated with increased discomfort (and possible need for sedation), longer procedure time, need for additional durable and disposable instruments, and increased cost. Other than being resource-intensive, TP-Bx is less familiar to the large majority of urologists, necessitating additional training for physicians and clinical staff. Perhaps the most important barrier is the lack of level 1 evidence and conflicting guidelines. The AUA guidelines, in contrast to the European guidelines, have a neutral stance, without favoring one procedure over the other. Emerging reports from observational studies have demonstrated infectious complication rates to be somewhat similar between the TR-Bx and TP-Bx approaches.[17,18] 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.

> "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."

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. ■

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SPECIAL AND MEMORABLE PATIENTS

A Urologist's Perspective: A Window Into Baseball

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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

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A UROLOGIST'S PERSPECTIVE: A WINDOW INTO BASEBALL

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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.

> "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."

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 individually 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.

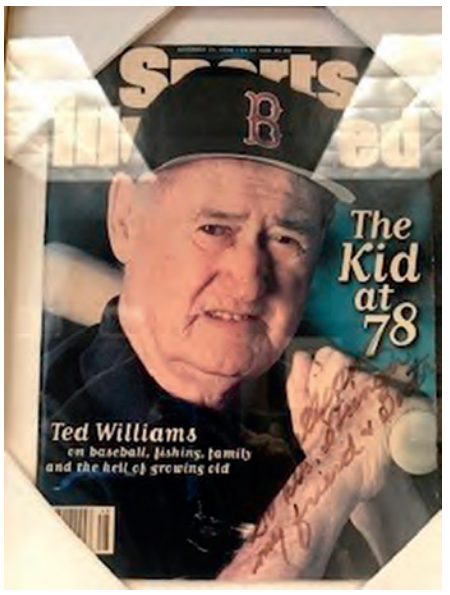

Figure. *Sports Illustrated* cover signed by Ted Williams to Dr Stringer.

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 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 to me on the front page of a *Sports Illustrated* issue (see Figure). Our relationship endured as a friendship and ended with my signature on his death certificate. Without a doubt, the cherished memories of our friendship live on. ■

PROSTATE CANCER

Should Same-day Discharge After Robotic Radical Prostatectomy Be the Standard of Care?

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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.[1,2] 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.

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.[3] Similarly Litwin et al reported that, following a clinical pathway to decrease length of stay (median 3 nights), there was no detrimental impact on 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."

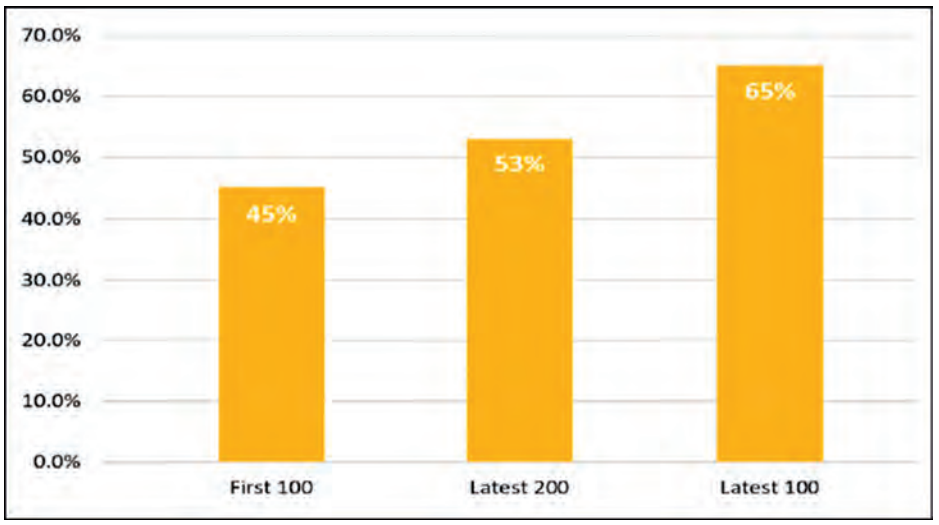

Figure. Increasing percentage of patients who elected same-day discharge after robotic prostatectomy. Reprinted with permission from Abaza R et al, *J Urol*. 2019;202(5):959.[4]

Almost 20 years later, Abaza et al described implementation of a same-day discharge (SDD) protocol.[4] 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.[5] 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.[6] 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

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SHOULD SAME-DAY DISCHARGE AFTER ROBOTIC RADICAL PROSTATECTOMY

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as SDD.[7] There were no significant clinicodemographic features 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 7.2% 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 consecutive radical prostatectomy cases with a 2.5% readmission rate.[8] 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 clinical burden. The critical component of SDD acceptance is preoperative patient counseling. Notably this is discussed extensively in the papers by Litwin[2] and Klein[3] et al as fundamental to patient acceptance 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.[4,8] Similarly, Ploussard et al reported 76% adherence with SDD protocols when discussed at the preoperative visit.[9] 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. ■

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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 stratification–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.[1,2] The new guidelines statements 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.[3]

Part I: Screening

In contrast to a purely age-based approach to PSA-based screening as recommended in the 2013 guideline, the current version emphasizes 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 suggesting utility of other biomarkers or imaging as first-line tests, PSA is still recommended as the first screening test.[4,5]

> "The new guidelines statements 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."

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 recommended 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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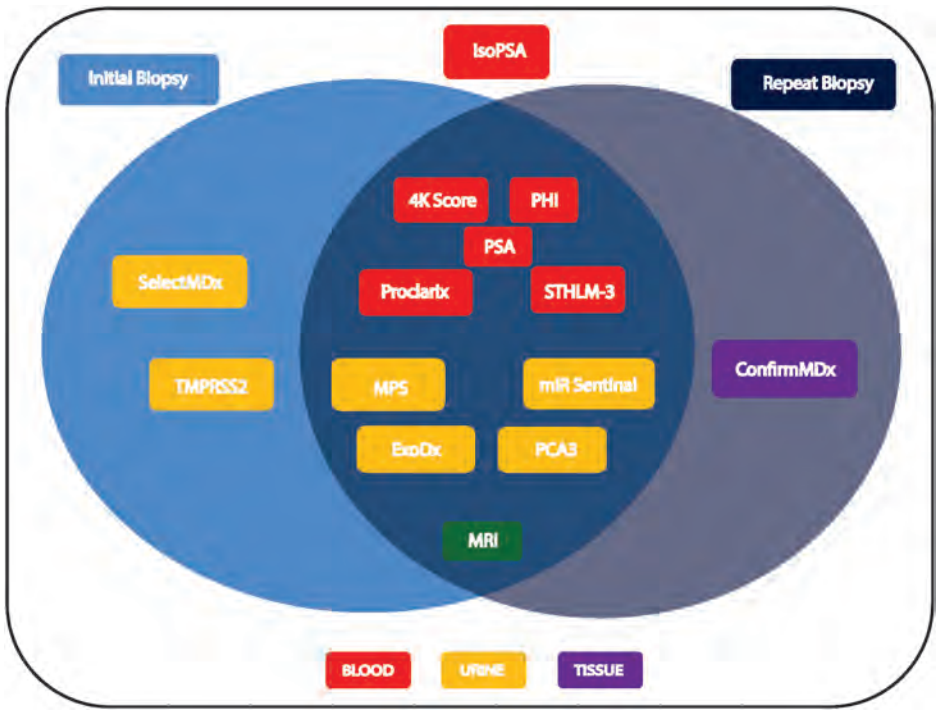

Figure. Biomarker and imaging tests in the initial and repeat prostate biopsy settings. MPS indicates MyProstateScore; MRI, magnetic resonance imaging; PHI, Prostate Health Index; PSA, prostate-specific antigen.

of high risk for detection of aggressive tumors.[6,7] 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.[8] 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.[9] Additional randomized trial results have suggested noninferiority of an MRI-targeted biopsy-only approach to screening for prostate cancer.[10,11] 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.[12] 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.[11,13]

The guidelines also address the numerous serum-, urine-, and tissue-based biomarkers available for identifying patients for prostate biopsy. 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[14,15] along with improved clinically significant cancer detection when using a targeted transperineal approach, the panel did not recommend preferential use of the transperineal technique as the data are still mixed.[16,17]

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

Both the European Association of Urology (EAU) guidelines[18] and the National Comprehensive Cancer Network (NCCN) guidelines[19] 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

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abnormal DRE doubles the risk of positive prostate biopsy.[20] 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 proceeding with a systematic biopsy in those with elevated risk, and the NCCN cautions that significant cancers can exist outside of MRI-identified targets. EAU guidelines also recommend performing 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. ■

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PROSTATE CANCER

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 to open 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 our outcomes were typically worse compared to other groups. Considering 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.[1] Prostate cancer death rates substantially declined in each congressional district with relative decline ranging from 25% to 68.3%. 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.[2]

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

Disparities in prostate cancer exist among men who are part of the Hispanic, American Indian, and Alaskan Native communities.[3] 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.[4] A recent meta-analysis revealed that Black and Hispanic men remain underrepresented in prostate cancer clinical trials.[5] Advocacy remains one of the keys to addressing disparities in prostate cancer.[6] Advocacy at the local, regional, and national level can have a profound impact on disparities in not only prostate, but other urological conditions. I encourage interested readers to consider attending the 2024 Annual Urology Advocacy Summit on Capitol Hill.

There is much work to do to address disparities in prostate cancer. Some evidence has shown that addressing disparities with one group could have an overall positive impact on the health of all. I believe that disparities in prostate cancer are not rooted in nature or nurture alone, but both. With further investigation of social determinants of health and targeted interventions we can contribute to the overall well-being of society. Our colleague, Dr Willie Underwood, is leading a broad discussion surrounding the impact of health care disparities in his current role as Chair of the American Medical Association Board of Trustees. I have been particularly encouraged by the actions of the Urology Care Foundation under the leadership of Dr Harris M. Nagler. The inaugural Urology Care Foundation Health Equity Fellowship, awarded to rising star Dr Randy Vince, will allow Dr Vince to continue his innovative work exploring social determinants of health and prostate cancer disparities.[7] Let's all support Dr Vince and others who are interested in this work. I make this plea, not as a fellow urologist, but as a member of a high-risk population and humble servant trying to help families that may suffer due to the loss of a loved one sooner than necessary. ■

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

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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]

Learn more. Visit **PSADoubling.com**

AUA = American Urological Association; BCR = biochemical recurrence; NCCN = National Comprehensive Cancer Network; nmCSPC = non-metastatic castration-sensitive prostate cancer; PSA = prostate-specific antigen.

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