American Urological Association

AUANews

AUGUST 2023

VOLUME 28 | ISSUE 8

AUANews.net

THE OFFICIAL NEWSMAGAZINE OF THE AMERICAN UROLOGICAL ASSOCIATION

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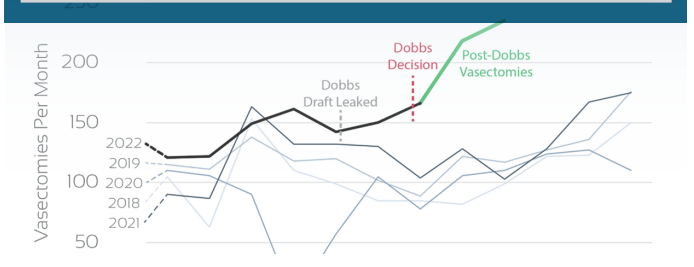

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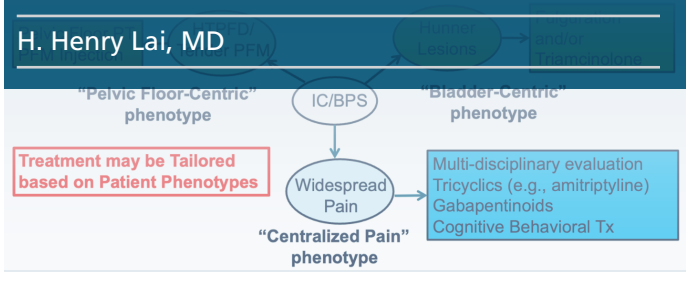
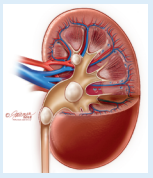


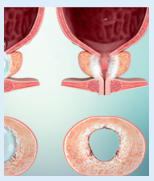
Surgical Techniques: Robotic Single-port Extraperitoneal Radical Prostatectomy

Ahmed Ghazi, MD, FEBU, MHPE

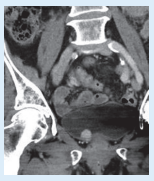
COMING SOON IN THE AUGUST ISSUE OF *AUANews*Extra



AUA2023 TAKE HOME MESSAGES: Endourology/Kidney Stones



AUA2023 TAKE HOME MESSAGES: Benign Prostatic Hyperplasia/Lower Urinary Tract Symptoms



A Rare Presentation of a Nonfunctioning Bladder Paraganglioma

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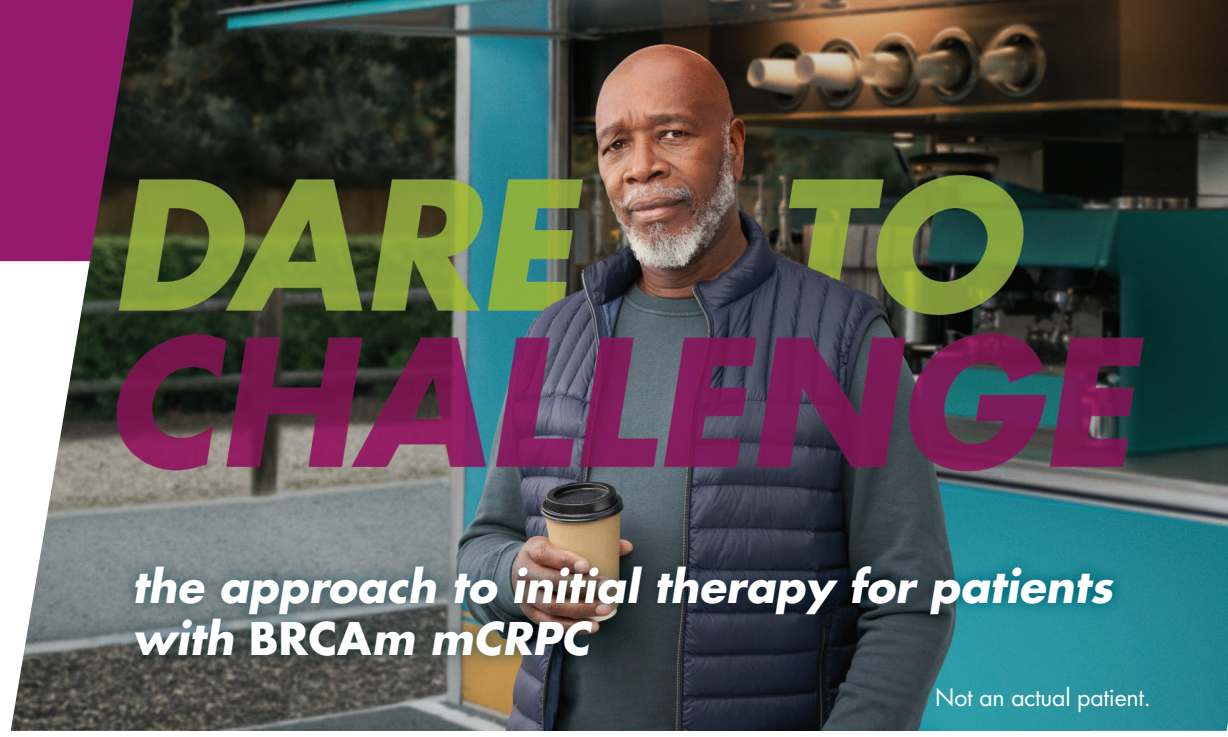


NOW APPROVED

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

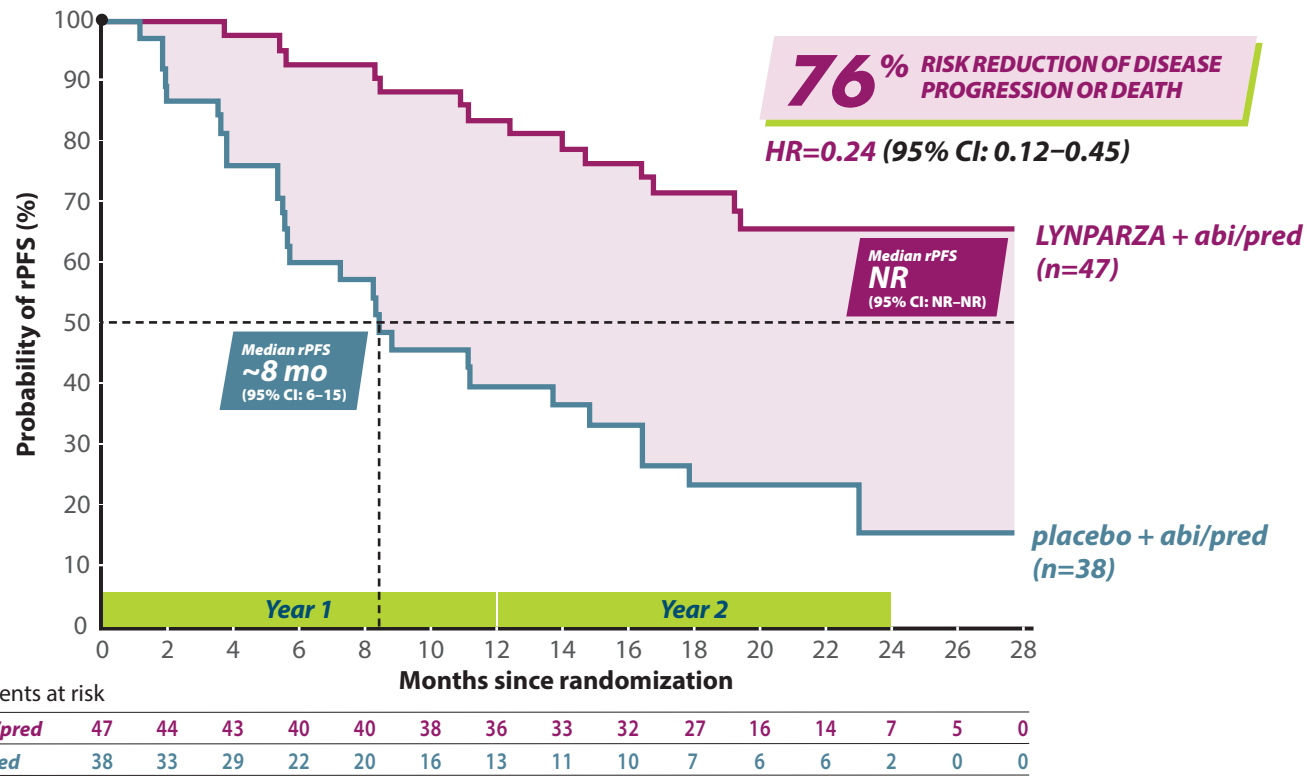
Most common adverse reactions (Grades 1-4) in ≥10% of patients who received LYNPARZA/abiraterone with a difference of ≥5% compared to placebo for **PROpel** were: anemia (48%), fatigue (including asthenia) (38%), nausea (30%), diarrhea (19%), decreased appetite (16%), lymphopenia (14%), dizziness (14%),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

August 2023, Volume 28 | Issue 8

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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.

Simultaneous Percutaneous Nephrolithotomy and Ureteroscopy for Bilateral Urolithiasis

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Bilateral urolithiasis is not an uncommon problem. Several studies have demonstrated the safety of same-session bilateral treatment with bilateral percutaneous nephrolithotomy (PCNL) and/or ureteroscopy (URS).[1-7] In an appropriately selected patient, these studies suggested performing same-session bilateral treatment of urolithiasis yields comparable stone-free and complication rates to staged procedures. This approach provides multiple advantages, including a single anesthetic, shorter cumulative operative time, fewer days in the hospital, and reduced cost. When performing a PCNL, the presence of a contralateral ureteral stone in a patient would compel most physicians to treat bilaterally, in efforts to alleviate or prevent symptoms. Recent findings from a multicenter, randomized, controlled trial further support bilateral treatment in the setting of a contralateral, asymptomatic renal stone.[8] The proactive treatment of asymptomatic contralateral stones was associated with a 75% lower incidence of stone relapse and a longer time to relapse without significant operative or perioperative morbidity compared to observation.[8]

A survey conducted by Rivera et al revealed 85% of endourologists were willing to perform bilateral simultaneous (BL-S) URS under the same anesthetic; however, only 38% had previously performed BL-S PCNL. For those respondents who did not perform bilateral PCNL, 10% would offer unilateral PCNL and contralateral URS as an alternative treatment option for patients.[9] This approach is optimal for patients with a large-volume stone burden on the planned PCNL side and a small- or intermediate-size contralateral stone burden (Figure 1).[9] This is a particularly attractive option for symptomatic patients on the contralateral side or those asymptomatic patients in whom there is a desire to reduce the likelihood of future stone events. Shared decision-making is crucial, and the factors influencing the surgical feasibility should be thoroughly evaluated.

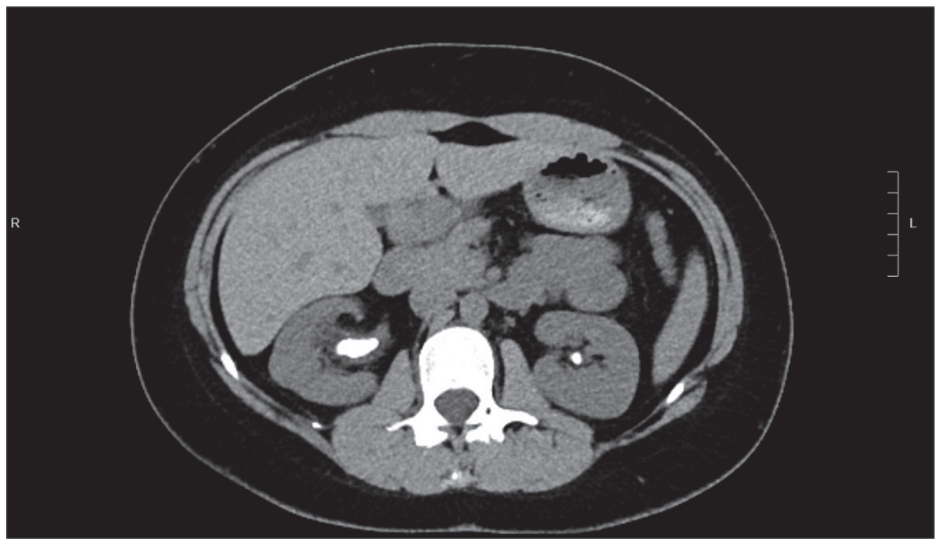

Figure 1. CT image of large (2.2 cm) right-sided stone burden and small (7 mm) left-sided stone burden.

Patient positioning and available equipment determine the feasibility of BL-S PCNL and URS. There is growing attention to the benefits of supine positioning for PCNL, including the ability to simultaneously access the contralateral renal unit; however, the majority of surgeons in the United States perform PCNL in the prone position. A split-legged prone operating table can facilitate simultaneous percutaneous treatment, while also performing contralateral treatment via retrograde URS. Setup for simultaneous bilateral treatment does not add a significant amount of preparation time and can allow 2 surgeons to operate in tandem for patients in the prone position. The equipment necessary for simultaneous bilateral treatment includes 2 cameras and/or digital scopes, 2 irrigation setups, and at least 2 monitors; thus, feasibility of this somewhat resource-heavy procedure is institution dependent (Figure 2).

Simultaneous bilateral treatment has been shown to have shorter cumulative operative times compared to staged procedures. A comparative study by Shen et al showed a shorter overall operative time when comparing BL-S PCNL and URS to staged treatment of patients with staghorn calculi and contralateral ureteral stones (123 vs 141 minutes).[4] Moreover, 2 experienced surgeons can operate concurrently, reducing operative time even further. Giusti et al demonstrated a mean operative time of 79 minutes when performing BL-S PCNL and URS operating on both renal units simultaneously.[3] While a shorter operative time is an important factor, the safety and efficacy of a simultaneous bilateral approach are of paramount importance.

With regard to efficacy, BL-S PCNL and URS have been shown to have stone-free rates as high as 92% and most importantly are comparable to a staged approach.[2,4,7] However, the definitions of stone-free vary in the literature, which limits its utility as a primary outcome measure.

When evaluating safety, the increased operative time under a single anesthetic and operating on both renal units have the potential to increase complications. Minor and major complication rates have been reported at 22% and 1.4% for BL-S URS, and 27% and 6.4% for BL-S PCNL, respectively.[10] Comparative and prospective studies for BL-S PCNL and URS remain limited. Although only small studies have been reported, overall complications ranged from 11%-18% with a 1% rate of major complications (Clavien grade III or higher).[3,4,7] Moreover, much of the literature on BL-S PCNL, URS, or PCNL+URS reports on a case basis, rather than per renal unit, which can potentially overestimate the reported complications. While

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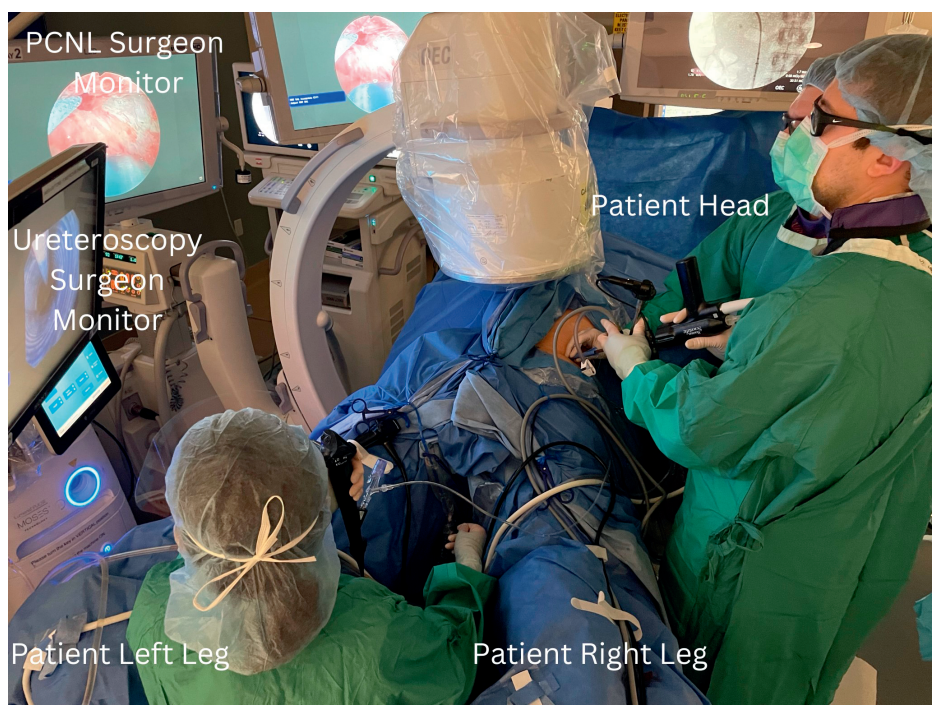

Figure 2. Split-legged prone table operative setup for tandem bilateral surgery. PCNL indicates percutaneous nephrolithotomy.

SIMULTANEOUS PERCUTANEOUS NEPHROLITHOTOMY

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the safety and efficacy of BL-S PCNL and URS appear to be comparable to a staged approach, the impact of BL-S treatment on patient quality of life has not been investigated. This area not only warrants future investigation, but also should be included in preoperative counseling with patients.

Given these considerations, tailoring the approach to each individual patient is critical. Shared decision-making after determining the surgical feasibility and potential advantages for BL-S PCNL and URS is of utmost importance. To guide this process, ideal candidates for BL-S PCNL and URS should have favorable calyceal anatomy with anticipated single-tract access, predicted operative time of less than 3 hours, limited comorbidities, favorable overall renal function, and successful completion of surgery on the first planned side without complications.

A combined BL-S PCNL and URS approach for patients with bilateral urolithiasis can achieve high stone-free rates, potentially shorter operative times, and a similar safety profile to other BL-S urolithiasis surgeries and staged approaches, though further investigations particularly focused on describing patient quality of life are warranted. ■

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Dr ChatGPT: Transforming Urological Care with the Integration of AI-powered Large Language Models

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New technology, like any transformative change, can inspire a range of emotions among users from curiosity and excitement to anxiety and resistance. The long-awaited advancements of artificial intelligence (AI) have suddenly been thrust upon the general public, urologists included, with the explosion of large language models (LLMs), machine-learning algorithms that understand, interpret, and respond to human language. Much like the early years of uncertainty with electronic medical records (EMRs), LLMs and AI are still in their infancy as medical tools. Rather than resist their use, however, we can better shape their evolution and integration into urology by embracing these technologies.

Over the past several months, several innovative LLM platforms have been launched, including ChatGPT, Bard, and Bing AI, each showcasing the remarkable capabilities of AI. The adoption of these advanced AI chatbots has been extraordinary, with Open AI's ChatGPT amassing over 100 million users within 2 months of its public release in November 2022, making it the fastest-growing application in history.[1] Despite its young age, it has already passed the SAT,[2] MCAT (Medical College Admission Test),[3] USMLE (United States Medical Licensing Examination) Steps,[4] and urology (practice) board exam![5]

LLMs have the potential to augment care and reduce work burden, not replace providers. How best to apply these tools in urological practice is still evolving, and rapidly. In this article, we discuss the potential role of machine language models for patient-facing, physician-facing, and administrative applications and review their current limitations. As a medical specialty that commonly embraces new technologies (think robotics), we aim to pique curiosity with a more comprehensive understanding of LLMs.

What Is AI and an LLM?

AI, in a broad sense, refers to computer systems capable of performing intricate tasks that once required human input. Think IBM's Deep Blue, which defeated chess grandmaster Garry Kasparov in 1997. An LLM uses AI to perform self-supervised learning on a given set of data and subsequently performs a variety of natural language processing tasks, most commonly answering conversational questions. GPT4 (generative pretrained transformer), released in March, was trained on 170 trillion parameters from various books, websites, articles, and other publicly available sources (see Table). Compare that to 175 billion parameters for GPT3, which spurred the LLM fervor in November, and 1.5 billion parameters for GPT2 released in 2019. With more data points, the LLM output becomes more accurate and human-like.

After training on a data set, an LLM essentially works as a statistical model. When prompted, natural language processing reviews the prompt and generative AI replies with a word-by-word response based on patterns learned during training. User feedback is utilized to optimize future responses. Whether generating a research grant on postprostatectomy care or a Shakespearean prostatic hypertrophy soliloquy, the LLM employs the same techniques. The success of AI-powered LLMs, then, depends, ironically, on the quality of the human-input request.

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Table. Commonly Used Current Large Language Models

LLM	Developer	Public release	No. trained parameters	Cost
GPT3	OpenAI	November 2022	175 billion	Free
GPT4	OpenAI	March 2023	100 trillion	Paid subscription
Bing AI	Microsoft	February 2023	Not disclosed	Free
Bard	Google	March 2023	137 billion	Free

Abbreviations: AI, artificial intelligence; GPT, generative pretrained transformer; LLM, large language model.
GPT3 and GPT4 are both versions of ChatGPT.

DR ChatGPT: TRANSFORMING UROLOGICAL CARE

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Integrating LLMs into Urological Care

Broadly speaking, LLMs can be applied to urological care in 3 different applications: patient-facing, provider-facing, and administrative. Prompts can be used to enhance communication and collaboration, increase efficiency, and improve patient outcomes.[6,7] LLMs are particularly good at repetitive writing tasks. Opportunities for implementation are only limited by the creativity of our prompts (Gabrielson et al article contains excellent examples[8]). Below are potential applications of LLMs in urological practice.

- Patient-facing
  - *Patient education*: Provide patients with personalized and accessible information about urological conditions, treatment options, and potential side effects, empowering them to make informed decisions and promote engagement.
  - *Symptom management*: Answer questions about symptoms with personalized suggestions for management, such as lifestyle modifications, medications, or a health care provider evaluation. May identify early warning signs and enable intervention.
- Provider-facing
  - *Clinical decision support*: Assist physicians with clinical questions by referencing clinical guidelines, research, and best practices. Can improve diagnostic accuracy, facilitate evidence-based decision-making, and promote standardized care pathways.
  - *EMR integration*: Can provide direct access to clinical decision support as above. Also can serve as first-line response to online EMR patient inquiries, decreasing response times, improving patient satisfaction, and saving time for health care providers.[9]
  - *Professional education*: Serve as a platform for ongoing professional development, offering access to educational materials.
- Administrative
  - *Letter generation*: Write prompted letters for appointments, prior authorizations, and denial appeals, reducing burden on administrative staff.
  - *Educational content creation*: Create educational content about urological conditions and treatments tailored to specific audience and needs (eg, pamphlet, website, media request, social media posting).

LLM Limitations and Warnings

Despite their sophisticated architecture, machine learning models are not faultless. LLMs lack formal medical training. The quality of output content is directly tied to the quality of the training data it has been exposed to. Any biases or inaccuracies in the training data may be mirrored in the output, so they may provide unreliable health-related information.[6] In a query of 3 AUA male sexual dysfunction guidelines (erectile dysfunction,

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Peyronie's disease, and disorders of ejaculation), 30% and 36% of GPT3 responses were inaccurate or incomplete, respectively (unpublished data).

These models do not retrieve data from a preexisting database as a search engine would, instead functioning as tools that generate output by approximating an ideal response based on learned patterns and associations. Thus an LLM may generate seemingly plausible but incorrect responses. This phenomenon, known as the hallucination effect, is a prevalent issue in natural language processing models.[10] LLMs have even been known to quote reference citations that do not exist.[11]

The World Health Organization recently issued a statement warning of bias and misinformation in AI health care applications.[12] In March, numerous international figures, including several tech thought leaders, in an open letter called for an immediate pause in LLM development until safety protocols can be established.[13] Until there is a formal body overseeing the development and use of LLMs in health care, it is imperative for end users to review the accuracy and completeness of generated content. Patients must also be cautioned of potentially misleading medical information as not all current LLMs provide this disclaimer.

In summary, LLMs offer the potential for improving patient care and reducing clinical and administrative workloads as detailed in 3 application categories–patient-facing, provider-facing, and administrative. LLM-generated output should be used as a framework and fact-checked for content given the current limitations of LLMs. Regardless, these AI tools are here to stay. As a wise senior urologist once defended health care evolution: "You're either growing or you're fading." In this article, hopefully we are encouraging growth. ■

None of this text has been generated by AI, just the human kind.

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SEPTEMBER 2023 | PROSTATE CANCER FOCUS ISSUE

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Closing Gender Gap in Family Planning Post-Dobbs

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In June 2022 the United States Supreme Court issued a ruling in the case *Dobbs v. Jackson Women's Health Organization* that overturned *Roe v. Wade*, the 1973 ruling establishing the federally protected right to abortion.[1] Despite wide support for female reproductive autonomy through decades of national polling, each state now had the ability to set its own abortion-related laws.[2] The ruling resulted in a profound and unanticipated impact on males seeking vasectomies. Following widespread media coverage of the phenomenon, Sellke et al found that Google searches for "vasectomy" spiked fourfold on the day after the ruling as compared to the past 5 years.[3] Patel et al had similar findings based on an analysis of Google search trends, particularly in states with fewer urologists and abortion bans.[4] The Cleveland Clinic Foundation was then the first to confirm an actual rise in vasectomy consultation and volume after the *Dobbs* ruling.[5] A retrospective analysis of the 13-hospital network demonstrated a doubling of median monthly vasectomy volume immediately following *Dobbs*, from 104 to 218 vasectomies performed ($P = .03$; see Figure). Study authors also found a rise in childless men (16.9% vs 8.6%) and men under 30 years old (23.9% vs 10.3%) seeking vasectomy post *Dobbs*.

The influence of the *Dobbs* ruling on family planning cannot be understated. While women have historically borne the brunt of contraceptive decision-making, the current legal climate has galvanized men to take on this burden. The reversal in attitudes is particularly striking in a country which had declining rates of vasectomy over the prior decade.[6] Increased conversation about reproductive rights may have prompted motivated men to seek control of their reproductive capabilities much earlier than their older counterparts.[7]

While we continue to learn the long-term effects of the Dobbs ruling on population demographics, physicians must keep advocating for and practicing the highest standards of medicine. In an increasingly fraught political landscape, the doctor-patient relationship may be one of the only places where patients retain autonomy in their own medical care. ■

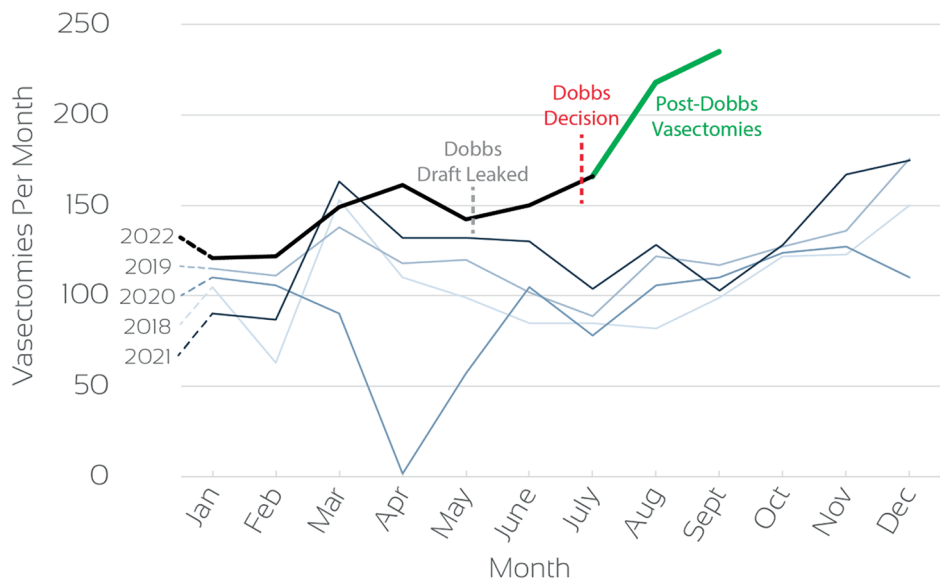

Figure. Vasectomy procedural volume from 2018-2022. Dobbs decision leak is noted in gray, and the final Dobbs decision is highlighted in red. The green line delineates the 2022 post-Dobbs cohort.

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AUA2023: REFLECTIONS

AUA2023 Plenary Session: Case-based Panel Discussion of Chronic Pelvic Pain

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During the AUA2023 plenary session, Dr Henry Lai led a panel discussion on "Case-based Discussion of Chronic Pelvic Pain" along with panelists Dr Elise De from Albany Medical Center, Dr Priyanka Gupta from the University of Michigan, and Dr Lindsey McKernan from Vanderbilt University Medical Center. The cases illustrated the take-home message that the treatment of interstitial cystitis (IC)/bladder pain syndrome (BPS) may be tailored based on specific patient phenotypes (Figure 1).

The first case, Maria, is a 60-year-old female with a 1-year history of bladder pain that is worsened with bladder filling. The pelvic pain is associated with a constant urge to urinate, urinary frequency, and dyspareunia. Urinalysis and urine culture are negative, and postvoid residual is 20 cc. Voiding diary reveals frequent, low-volume voided volumes. Examination is unremarkable.

The clinical presentation is consistent with IC/BPS, which is defined in the AUA Guideline as having "pain, pressure, or discomfort, perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks' duration, in the absence of infection or other identifiable causes."[1] IC/BPS is a diagnosis of exclusion. Confusable conditions that give rise to similar symptoms should be ruled out. Dr De presented a comprehensive list of differential diagnoses or confusable conditions to exclude (see Table).

Per the updated AUA Guideline, men or women over the age of 50 years should consider cystoscopy to evaluate for Hunner lesions.[1] Maria underwent office cystoscopy, and was found to have Hunner lesions (Figure 2). She was treated with fulguration and triamcinolone injection into the Hunner lesions, and improved remarkably. IC patients with Hunner lesions on

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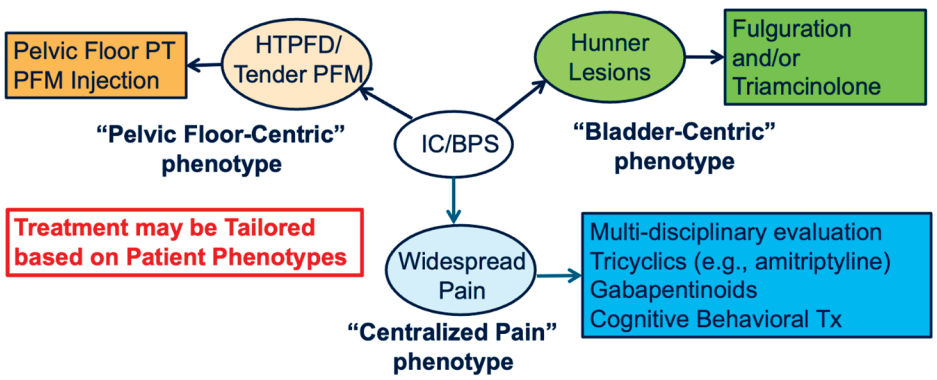

Figure 1. Phenotype-driven treatment of interstitial cystitis/bladder pain syndrome (IC/BPS). HTPFD indicates high-tone pelvic floor dysfunction; PFM, pelvic floor muscle; PT, physical therapy; Tx, therapy.

cystoscopy have a bladder-centric phenotype, and can be offered fulguration and/or triamcinolone injection that specifically targets their Hunner lesions (Figure 1).

The second case, Kysha, has similar clinical presentation except that she has no Hunner lesions on cystoscopy, and thus she has BPS instead of ulcerative IC. Her pelvic floor examination is remarkable for tenderness on palpation. Dr Gupta gave a presentation on the evaluation and management of high-tone pelvic floor dysfunction.

Up to 85% of IC/BPS patients have pelvic floor tenderness on pelvic examination. Standardized pelvic exam may be performed vaginally in women or transrectally in men as previously described (Figure 3).[2] Pelvic floor physical therapy is the gold standard and the backbone of any pelvic floor treatments.[3] Additional treatment options include vaginal valium or amitriptyline suppository, neuromodulation, or injections into the pelvic floor muscle. Dr Gupta uses a curved nasal trumpet (7-inch spinal needle) which allows the needle to pass around the pubic bone. Injections are performed using a standard template immediately behind the pubic bone, at the level of the ischial spine, and at 1, 3, 5, 7, 9, and 11 o'clock to target the obturator internus and externus muscles and the iliococcygeus, pubococcygeus, and puborectalis muscles. At the 5 and 7 o'clock proximal locations a pudendal nerve block is performed. The injection solution contains 25 cc 0.5% bupivacaine mixed with 1 cc

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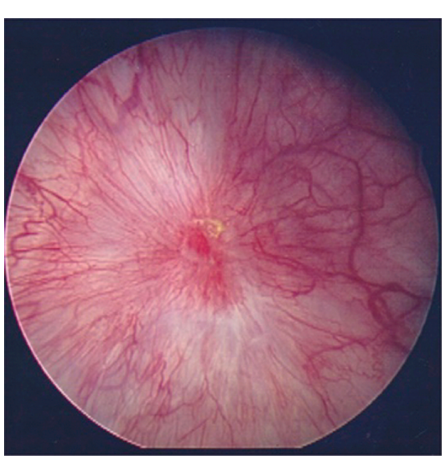

Figure 2. Classic Hunner lesions, as described by Ronstrom and Lai.[7]

Table. Differential Diagnosis of Interstitial Cystitis/Bladder Pain Syndrome

Differential diagnosis/confusable condition	Can be distinguished from IC/BPS by
Overactive bladder	Symptoms (urgency incontinence vs pain)
Infectious etiology	Cultures
Pelvic malignancy, radiation, chemotherapy	Medical history, imaging, cystoscopy
Vaginal mesh complication	Surgical history, pelvic exam, cystoscopy
Pelvic organ prolapse	Pelvic exam
Urethral diverticulum	Pelvic exam, urethral MRI
Distal ureteral stone, bladder stone	Stone history, CT stone protocol, cystoscopy
High-tone pelvic floor dysfunction	Pelvic floor exam (Figure 2)
Pubic diastasis	Pain worse with weight bearing, imaging
Osteitis pubis	Pain worse with adduction, imaging
Pelvic venous congestion syndrome	Pain worse with standing, pain less in morning
Endometriosis	Pain with menstrual cycles, laparoscopy
GI causes: inflammatory bowel disease, irritable bowel syndrome	GI symptoms, pain worse with change in bowel habits, endoscopy, imaging
Neurological causes: nerve entrapment, myopathy, sacral tumor, Tarlov cyst	Neurological symptoms, pain radiation along dermatome or nerve distribution, imaging

Abbreviations: CT, computerized tomography; GI, gastrointestinal; IC/BPS, interstitial cystitis/bladder pain syndrome; MRI, magnetic resonance imaging.

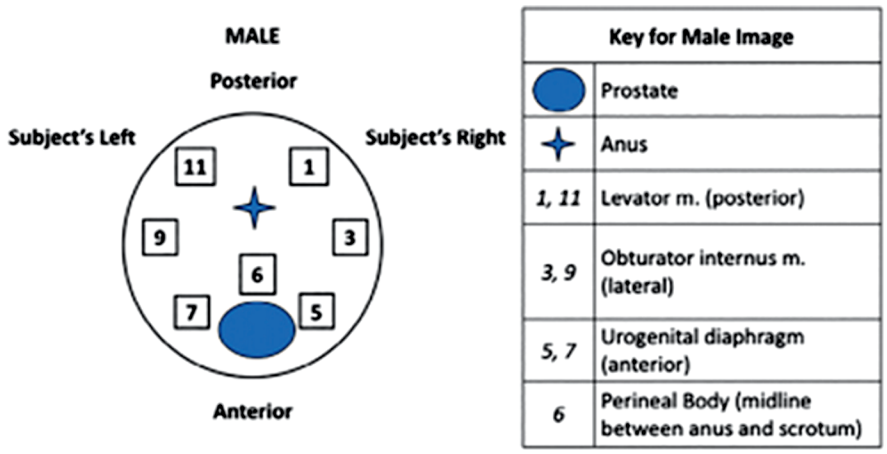

Figure 1. Diagram for male pelvic muscle examination. Sites of palpation, performed through the rectum, with subject's anterior surface facing down relative to examiner. Numbers correspond to clock-face positions. (Color version available online.)

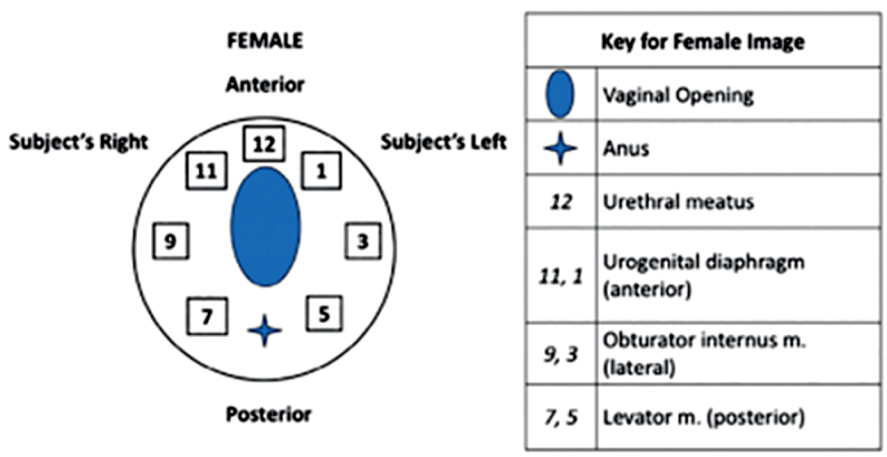

Figure 2. Diagram for female pelvic muscle examination. Sites of palpation, performed through vagina, with subject's anterior surface facing up relative to examiner. Numbers correspond to clock-face positions. (Color version available online.)

Figure 3. Standardized pelvic examination templates in men and women, as described by Gupta et al.[2]

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40 mg triamcinolone. Two cc are injected at each location with 3 cc for the pudendal block. Injections may repeat every 6 to 8 weeks and can be done in the clinic or the operating room. Several studies have demonstrated efficacy in women with pelvic floor hypertonicity with tenderness, including intralevator injection of 100 to 300 U onabotulinum toxin A.[4,5] Patients with pelvic floor tenderness have a pelvic floor-centric phenotype and can be offered pelvic floor therapies that specifically target their pelvic floor (Figure 1).

The third case, Steve, is a 20-year-old male with bladder pain for 5 years. He is a graduate student, but because of his pain, he is disengaged and underperforming. He avoids relationships due to sexual pain and performance concerns. He is no longer active, and is depressed.

Dr McKernan discussed psychological approaches to manage chronic pelvic pain. Some patients may benefit from psychological referrals, such as those with red flags (eg, anxiety or depression affecting the ability to follow through with treatments, intense emotional response to symptoms, insomnia or nightmares, distress or avoidance, active trauma, or symptoms of posttraumatic stress disorder). It is important to approach with a multidisciplinary team (urology, psychology, psychiatry, physical therapy, pain management, etc). Steve was offered 20 sessions of cognitive behavioral therapy, which aimed to increase his pain coping skills, motivate him for treatment engagement and adherence, and address his depressive symptoms. Generally, patients with localized pain likely respond well to relaxation-based interventions, flare management, and having enhanced coping skills. Psychological intervention and a multidisciplinary approach may be most appropriate for patients with widespread pain or centralized presentation. Even when the pain intensity does not improve, secondary benefits may be realized in terms of improvement in quality of life, coping, and self-efficacy important to a person's well-being.

In addition, Steve also has widespread pain when a body pain map is administrated (Figure 4). Dr De discussed that widespread pain points to a systemic pathology and that some patients may have small-fiber polyneuropathy.[6] Dr Gupta emphasized the importance of multidisciplinary care in patients with widespread pain or systemic presentation. IC/BPS patients with widespread pain likely have centralized pain phenotype. They can be offered multidisciplinary treatments, medications that address their systemic pain such as amitriptyline or gabapentinoids, and/or psychosocial intervention such as cognitive behavioral therapy.

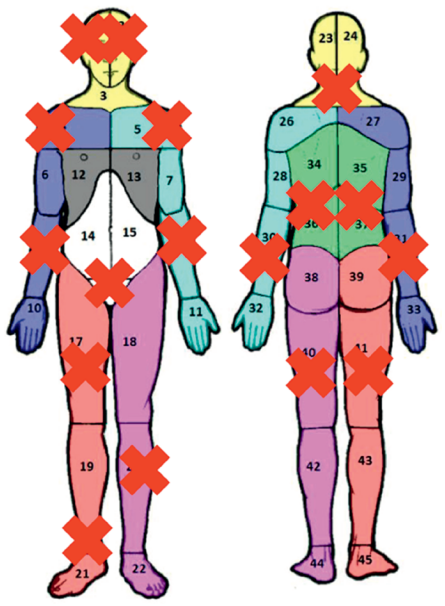

Figure 4. Widespread pain in interstitial cystitis/bladder pain syndrome, as mapped by Lai et al.[8]

In summary, the treatment of IC/BPS may be tailored based on specific patient phenotypes–bladder-centric vs pelvic floor-centric vs centralized pain phenotype (Figure 1). ■

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AUA2023: REFLECTIONS

Surgical Techniques: Robotic Single-port Extraperitoneal Radical Prostatectomy

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Robotics in urological surgery has increasingly been adopted due to the advantages over standard laparoscopy. Similarly, a shift toward robotic single-site surgery was observed to further decrease the operative morbidity.[1] The da Vinci SP is a robotic platform purpose-built for robotic SP surgery that shares multiple features with prior multiport da Vinci platforms. However, the SP robot includes a redesigned single 25-mm multichannel port accommodating an 8-mm articulating robotic camera and three 6-mm double-jointed articulating robotic instruments, a guidance system that allows the surgeon to know the location and movement of each instrument, 360° anatomical access from a single pivot point, and an extra clutch that gives the option to control the camera and the robotic arms as a single unit or independently.

Additional features and tips will be discussed in the context of an extraperitoneal robotic radical prostatectomy.[2] Following anesthesia, the patient is positioned completely supine with only 5-10° Trendelenburg (Video). A single 3-cm longitudinal midline incision is made midway between the umbilicus and pubic symphysis. The abdominal planes are carefully dissected to the anterior rectus fascia, where a 4- to 5-cm staggered fascial incision is made caudal to the skin incision (see Figure). An index finger is introduced under the anterior rectus fascia toward the pubic symphysis to create a space in the preperitoneal cavity using gentle sweeping motions. The balloon dilator is not required for SP extraperitoneal access due to the caudal incision and only a single midline port with smaller working radius. The inner ring of an access port is inserted in the created space, and the "fishbowl" component housing a 25-mm SP short entry guide multichannel cannula is attached to the external ring. An AirSeal tubing is attached to the access port for insufflation (optimal but not mandatory) to a pressure of 12 mm Hg. An additional (plus-1) 8-mm AirSeal assistant port can be placed in a "sidecar" fashion, where the port is inserted into the same skin incision but into a separate fascial incision. The multichannel cannula allows the built-in floating docking to gain the 10-cm clearance, deploying the instruments with the triangulation required. Instruments are introduced in the following orientation: hot monopolar scissors (3 o'clock), hot Maryland bipolar grasper (9 o'clock), articulating camera (12 o'clock), and hot fenestrated

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SURGICAL TECHNIQUES: ROBOTIC SINGLE-PORT EXTRAPERITONEAL RADICAL PROSTATECTOMY

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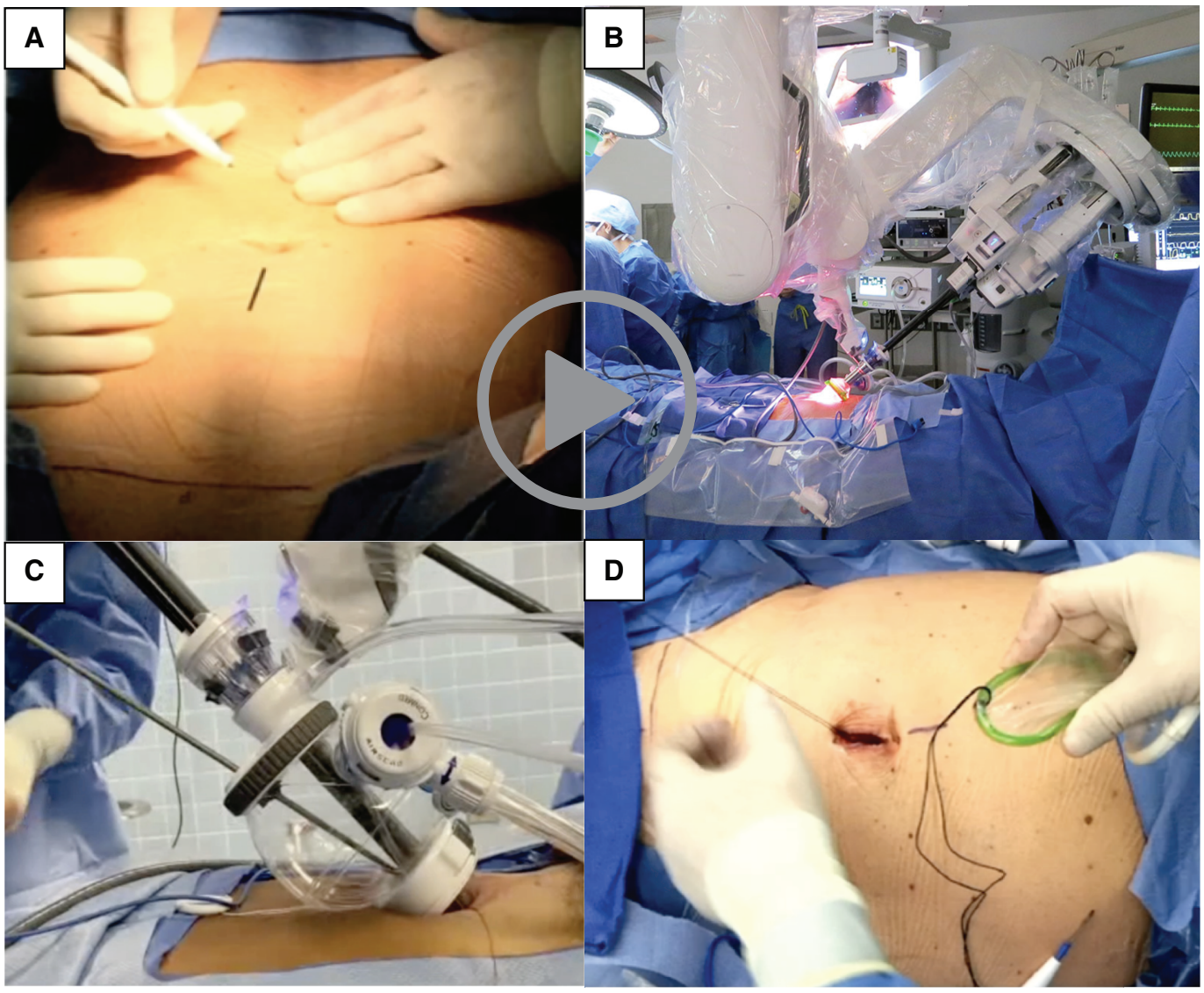

Figure. A, Incision. B, Patient positioning. C, Port placement. D, Specimen retrieval and closure.

bipolar grasper (6 o'clock). Personally, my preference is to have the fenestrated bipolar vs the Cadiere grasper for retracting as it allows interchange of cautery instruments during the procedure. Additional instruments include 2 needle holders and the 5-mm robotic Weck clip applier. The flexible tip of a remotely operated suction irrigation is introduced through the access port and manipulated by the surgeon via a foot pedal. Sutures knotted to the tip of the suction facilitate manipulation of the suction. In cases of no assistance, cautery utilization and meticulous hemostasis help maintain a clear field, limiting the need for continuous suction manipulation.

In this approach, the surgeon lands directly on the prostate rather than dissecting and mobilizing the bladder. The extraperitoneal space is further developed under direct vision via the robotic instruments with care to prevent dropping of the inferior epigastric vessels. The fat overlying the prostate is dissected, and the anterior prostate adequately exposed. The endopelvic fascia is incised and the deep venous complex is ligated with a GS-22 V-Loc suture. The half-circle 27-mm needle helps avoid collisions of closely positioned instruments during suturing. During prostatovesical junction dissection, adequate traction of the bladder is maintained by the fenestrated bipolar grasper at the 6 o'clock position. The prostate was dissected in an antegrade fashion using electrocautery with the camera orientation changed to the 30° down orientation using the adjust feature, activated either by the camera pedal+clockwise rotation of the right master-control or pressing cobra mode on the console touch display. Once the catheter is visible, a Keith straight needle is introduced percutaneously superior to the pubis and passed through the catheter side holes for retracting the prostate upward. The posterior layer of Denonvilliers' fascia is incised. My preference is to exchange both bipolar instruments with the fenestrated bipolar grasper at 9 o'clock to grasp the vas deferens and seminal vesicles upward, which are dissected en bloc. The SP robot also has a function wherein the instruments can be rotated 180° (around the clock) within the working space to change instrument orientation so that the camera and fenestrated forceps trade positions. The posterior plane is best developed by changing the orientation of the camera to 30° upward. The prostatic pedicles are then clipped with the robotic 5-mm Weck clips using a rotating maneuver during application to improve clip engagement. The neurovascular bundles are dissected off the prostate bluntly if indicated. For optimal traction without instrument collision, frequent changes in the camera control and relocation with continuous advancement of retraction arm are often needed. On the right side, the 9 and 12 o'clock bipolar instruments are interchangeable as the working/retracting arm. The previously ligated dorsal venous complex is divided and the urethra is transected at the prostatic apex. The specimen is retrieved into the "fishbowl" without the need for a specimen bag; it can also be retrieved and inspected if needed. Lymphadenectomy is performed, requiring the translocation feature that moves the entire port and instruments to either side of the pelvic wall. An extended template can also be performed.[3] The vesicourethral anastomosis was performed using 2 connected CV-23 V-Loc sutures in a continuous fashion over an 18F silicon catheter. The proximally located wrist of SP instruments compared to multiport instruments limits the ability to throw suture at a full 90° (6 o'clock stitch). The multiple angulation points and the single point of entry reduce the lateral strength, and therefore sutures are better tightened in line to the camera rather than perpendicular. A drain is optional. The skin and fascial incision are closed after removing the access port.

Extraperitoneal single-port robot-assisted radical prostatectomy seems to be a safe and feasible surgical option for the treatment of localized prostate cancer. However, a learning curve could be attributed to the lack of bedside assistant, requiring additional tasks by the surgeon, eg, suctioning and retraction, as well as increased coordination between the instruments and the camera to compensate for a smaller overall field of view due to the shorter working distance between the articulating instruments and camera. ■

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