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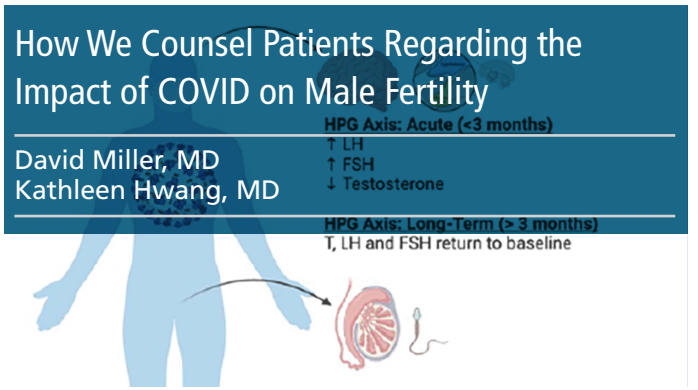

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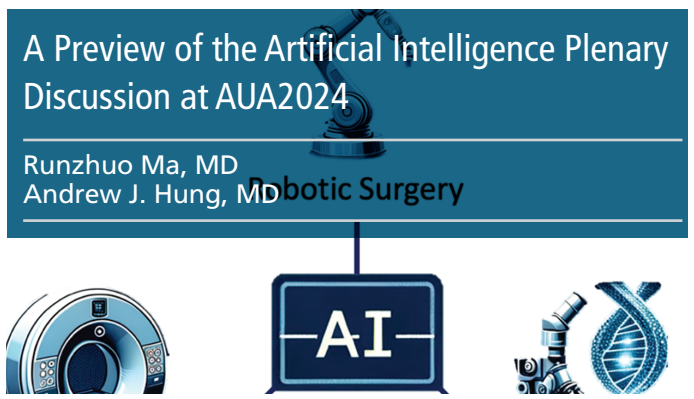

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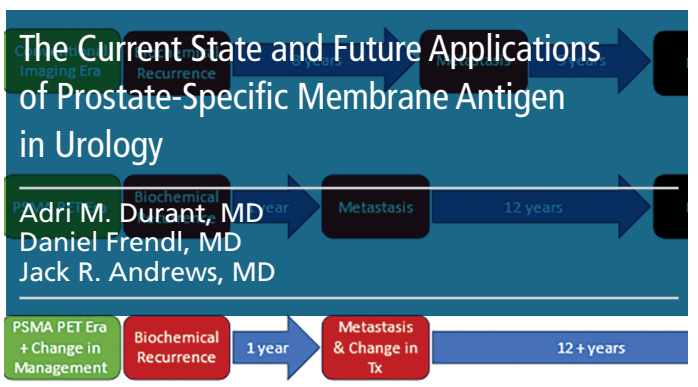

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NOW APPROVED IN nmCSPC WITH HIGH-RISK BCR[1]

NOW APPROVED IN nmCSPC WITH HIGH-RISK BCR[1]

Harness the power of XTANDI + GnRH therapy*† for your appropriate patients with **nmCSPC with high-risk BCR** for **proven efficacy benefits** vs placebo + GnRH therapy*[1]

BICR, blinded independent central review; **CI**, confidence interval; **ECOG**, Eastern Cooperative Oncology Group; **GnRH**, gonadotropin-releasing hormone; **HR**, hazard ratio; **NR**, not reached; **PSA**, prostate-specific antigen; **RP**, radical prostatectomy; **RT**, radiotherapy.
Metastasis-free survival was defined as the time from randomization to whichever of the following occurred first: 1) radiographic progression per BICR or 2) death.[1]

***Leuprolide.**[1]

†Patients with nmCSPC with high-risk BCR receiving XTANDI may be treated with or without GnRH therapy.[1]

‡Includes multiple terms.[1]

Important Safety Information

Warnings and Precautions

Seizure occurred in 0.6% of patients receiving XTANDI in eight randomized clinical trials. In a study of patients with predisposing factors for seizure, 2.2% of XTANDI-treated patients experienced a seizure. It is unknown whether anti-epileptic medications will prevent seizures with XTANDI. Patients in the study had one or more of the following predisposing factors: use of medications that may lower the seizure threshold, history of traumatic brain or head injury, history of cerebrovascular accident or transient ischemic attack, and Alzheimer's disease, meningioma, or leptomeningeal disease from prostate cancer, unexplained loss of consciousness within the last 12 months, history of seizure, presence of a space occupying lesion of the brain, history of arteriovenous malformation, or history of brain infection. Advise patients of the risk of developing a seizure while taking XTANDI and of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

Posterior Reversible Encephalopathy Syndrome (PRES) There have been reports of PRES in patients receiving XTANDI. PRES is a neurological disorder that can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. Discontinue XTANDI in patients who develop PRES.

Hypersensitivity reactions, including edema of the face (0.5%), tongue (0.1%), or lip (0.1%) have been observed with XTANDI in eight randomized clinical trials. Pharyngeal edema has been reported in post-marketing cases. Advise patients who experience any symptoms of hypersensitivity to temporarily discontinue XTANDI and promptly seek medical care. Permanently discontinue XTANDI for serious hypersensitivity reactions.

Ischemic Heart Disease In the combined data of five randomized, placebo-controlled clinical studies, ischemic heart disease occurred more commonly in patients on the XTANDI arm compared to patients on the placebo arm (3.5% vs 2%). Grade 3-4 ischemic events occurred in 1.8% of patients on XTANDI versus 1.1% on placebo. Ischemic events led to death in 0.4% of patients on XTANDI compared to 0.1% on placebo. Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue XTANDI for Grade 3-4 ischemic heart disease.

Falls and Fractures occurred in patients receiving XTANDI. Evaluate patients for fracture and fall risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents. In the combined data of five randomized, placebo-controlled clinical studies, falls occurred in 12% of patients treated with XTANDI compared to 6% of patients treated with placebo. Fractures occurred in 13% of patients treated with XTANDI and in 6% of patients treated with placebo.

Embryo-Fetal Toxicity The safety and efficacy of XTANDI have not been established in females. XTANDI can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment with XTANDI and for 3 months after the last dose of XTANDI.

Adverse Reactions (ARs)

In the data from the five randomized placebo-controlled trials, the most common ARs (≥ 10%) that occurred more frequently (≥ 2% over placebo) in XTANDI-treated patients were musculoskeletal pain, fatigue, hot flush, constipation, decreased appetite, diarrhea, hypertension, hemorrhage, fall, fracture, and headache. In the bicalutamide-controlled study, the most common ARs (≥ 10%) reported in XTANDI-treated patients were asthenia/fatigue, back pain, musculoskeletal pain, hot flush, hypertension, nausea, constipation, diarrhea, upper respiratory tract infection, and weight loss.

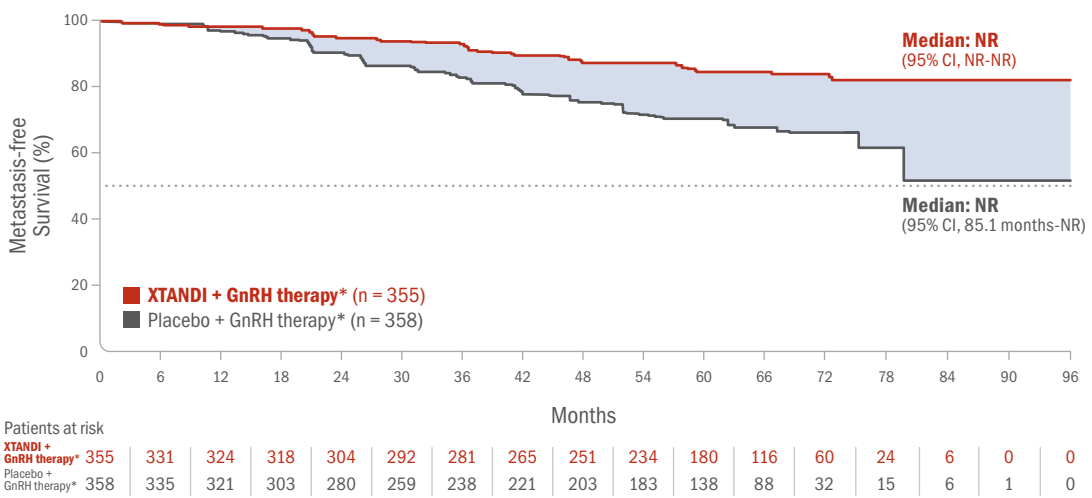
In AFFIRM, the placebo-controlled study of metastatic CRPC (mCRPC) patients who previously received docetaxel, Grade 3 and higher ARs were reported among 47% of XTANDI-treated patients. Discontinuations due to ARs were reported for 16% of XTANDI-treated patients. In PREVAIL, the

XTANDI is indicated for the treatment of patients with nonmetastatic castration-sensitive prostate cancer (nmCSPC) with biochemical recurrence at high risk for metastasis (high-risk BCR), metastatic castration-sensitive prostate cancer (mCSPC), or castration-resistant prostate cancer (CRPC).[1]

EMBARK was a randomized phase 3 trial that assessed the efficacy and safety of XTANDI + GnRH therapy* vs placebo + GnRH therapy* in 1068 patients with nmCSPC with high-risk BCR[1,2]

XTANDI + GnRH THERAPY* SIGNIFICANTLY IMPROVED METASTASIS-FREE SURVIVAL VS PLACEBO + GnRH THERAPY*[1]

METASTASIS-FREE SURVIVAL (PRIMARY ENDPOINT)[1]



IN nmCSPC WITH HIGH-RISK BCR[1]

METASTASIS-FREE SURVIVAL

58% **reduction in the risk of metastasis or death**

with XTANDI + GnRH therapy* vs placebo + GnRH therapy* (HR = 0.42 [95% CI, 0.30-0.61]; *P* < 0.0001)

- Number of events: 45 (12.7%) with XTANDI + GnRH therapy* vs 92 (25.7%) with placebo + GnRH therapy*[1]
- Median metastasis-free survival was not reached in either the XTANDI + GnRH therapy* arm or the placebo + GnRH therapy* arm[1]

Overall survival data were not mature at the time of metastasis-free survival analysis (12.2% deaths across the overall population of 1068 patients had been reported)[1]

In the EMBARK trial, the adverse reactions that occurred at ≥ 5% (Grade 1-4) or ≥ 2% (Grade 3-4) higher frequency in the XTANDI + GnRH therapy* arm than in the placebo + GnRH therapy* arm were hot flush (Grade 1-4: 69% vs 57%; Grade 3-4: 0.6% vs 0.8%), fatigue‡ (Grade 1-4: 50% vs 38%; Grade 3-4: 4% vs 1.7%), musculoskeletal pain‡ (Grade 1-4: 50% vs 43%; Grade 3-4: 4.8% vs 2.3%), fall (Grade 1-4: 21% vs 14%; Grade 3-4: 1.1% vs 1.1%), hemorrhage‡ (Grade 1-4: 20% vs 15%; Grade 3-4: 3.4% vs 1.7%), fracture‡ (Grade 1-4: 18% vs 13%; Grade 3-4: 4% vs 2.5%), diarrhea‡ (Grade 1-4: 15% vs 9%; Grade 3-4: 0.6% vs 0.8%), cognitive disorder‡ (Grade 1-4: 10% vs 4.8%; Grade 3-4: 0.3% vs 0.6%), osteoarthritis (Grade 1-4: 6% vs 4.2%; Grade 3-4: 2.8% vs 0.6%), and syncope (Grade 1-4: 4.8% vs 2.3%; Grade 3-4: 4.2% vs 1.7%).[1]

Patient population: All patients had prior definitive therapy with RP or RT (including brachytherapy) with curative intent, or both; confirmation of nonmetastatic disease by BICR; screening PSA ≥ 1 ng/mL after RP (with or without RT) as the primary treatment for prostate cancer or at least 2 ng/mL above the nadir after prior RT only; PSA doubling time ≤ 9 months; testosterone ≥ 150 ng/dL; ECOG Performance Status 0-1 at screening.[1,2]

Exclusion criteria (select): prior/current distant metastasis; prior hormonal therapy generally not allowed except for short courses ≤ 36 months in duration and ≥ 9 months before randomization; suitable candidate for salvage RT if prior prostatectomy; prior cytotoxic chemotherapy/systemic biologic therapy, including immunotherapy, for prostate cancer; history of seizure or any seizure-predisposing condition; and clinically significant cardiovascular disease.[3]

Patients were offered a treatment suspension once at Week 37 if PSA was < 0.2 ng/mL at Week 36; treatment was reinitiated when PSA values increased to ≥ 2.0 ng/mL for patients with prior prostatectomy or ≥ 5.0 ng/mL for patients without prior prostatectomy. In the XTANDI + GnRH therapy* and placebo + GnRH therapy* arms, GnRH therapy* was also suspended.[1]

placebo-controlled study of chemotherapy-naive mCRPC patients, Grade 3-4 ARs were reported in 44% of XTANDI patients and 37% of placebo patients. Discontinuations due to ARs were reported for 6% of XTANDI-treated patients. In TERRAIN, the bicalutamide-controlled study of chemotherapy-naive mCRPC patients, Grade 3-4 ARs were reported in 39% of XTANDI patients and 38% of bicalutamide patients. Discontinuations with an AR as the primary reason were reported for 8% of XTANDI patients and 6% of bicalutamide patients.

In PROSPER, the placebo-controlled study of nonmetastatic CRPC (nmCRPC) patients, Grade 3 or higher ARs were reported in 31% of XTANDI patients and 23% of placebo patients. Discontinuations with an AR as the primary reason were reported for 9% of XTANDI patients and 6% of placebo patients.

In ARCHES, the placebo-controlled study of metastatic CSPC (mCSPC) patients, Grade 3 or higher ARs were reported in 24% of XTANDI-treated patients. Permanent discontinuation due to ARs as the primary reason was reported in 5% of XTANDI patients and 4% of placebo patients.

In EMBARK, the placebo-controlled study of nonmetastatic CSPC (nmCSPC) with high-risk biochemical recurrence (BCR) patients, Grade 3 or higher adverse reactions during the total duration of treatment were reported in 46% of patients treated with XTANDI plus leuprolide, 50% of patients receiving XTANDI as a single agent, and 43% of patients receiving placebo plus leuprolide. Permanent treatment discontinuation due to adverse reactions during the total duration of treatment as the primary reason was reported in 21% of patients treated with XTANDI plus leuprolide, 18% of patients receiving XTANDI as a single agent, and 10% of patients receiving placebo plus leuprolide.

Lab Abnormalities: Lab abnormalities that occurred in ≥ 5% of patients, and more frequently (> 2%) in the XTANDI arm compared to placebo in the pooled, randomized, placebo-controlled studies are hemoglobin decrease, neutrophil count decreased, white blood cell decreased, hyperglycemia, hypermagnesemia, hyponatremia, hyperphosphatemia, and hypercalcemia.

Hypertension: In the combined data from five randomized placebo-controlled clinical trials, hypertension was reported in 14.2% of XTANDI patients and 7.4% of placebo patients. Hypertension led to study discontinuation in < 1% of patients in each arm.

Drug Interactions

Effect of Other Drugs on XTANDI Avoid coadministration with strong CYP2C8 inhibitors. If coadministration cannot be avoided, reduce the dosage of XTANDI.

Avoid coadministration with strong CYP3A4 inducers. If coadministration cannot be avoided, increase the dosage of XTANDI.

Effect of XTANDI on Other Drugs Avoid coadministration with certain CYP3A4, CYP2C9, and CYP2C19 substrates for which minimal decrease in concentration may lead to therapeutic failure of the substrate. If coadministration cannot be avoided, increase the dosage of these substrates in accordance with their Prescribing Information. In cases where active metabolites are formed, there may be increased exposure to the active metabolites.

Please see adjacent pages for Brief Summary of Full Prescribing Information.

References: 1. XTANDI [package insert]. Northbrook, IL: Astellas Pharma US, Inc. **2.** Freedland SJ, de Almeida Luz M, De Giorgi U, et al. Improved outcomes with enzalutamide in biochemically recurrent prostate cancer. N Engl J Med 2023;389(16):1453-65. **3.** Freedland SJ, De Giorgi U, Gleave M, et al. A phase 3 randomised study of enzalutamide plus leuprolide and enzalutamide monotherapy in high-risk non-metastatic hormone-sensitive prostate cancer with rising PSA after local therapy: EMBARK study design. BMJ Open (Epub) 08-12-2021.

START WITH XTANDI NOW

astellas ONCOLOGY

Pfizer Oncology

Xtandi® (enzalutamide) 40 mg capsules

Xtandi® (enzalutamide) 40 mg tablets | 80 mg tablets

XTANDI® (enzalutamide) capsules, for oral use
XTANDI® (enzalutamide) tablets, for oral use

Initial U.S. Approval: 2012

BRIEF SUMMARY OF PRESCRIBING INFORMATION

The following is a brief summary. Please see the package insert for full prescribing information.

INDICATIONS AND USAGE

XTANDI is an androgen receptor inhibitor indicated for the treatment of patients with:

- castration-resistant prostate cancer
- metastatic castration-sensitive prostate cancer
- nonmetastatic castration-sensitive prostate cancer with biochemical recurrence at high-risk for metastasis

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Seizure

Seizure occurred in 0.6% of patients receiving XTANDI in eight randomized clinical trials. In these trials, patients with predisposing factors for seizure were generally excluded. Seizure occurred from 13 to 2250 days after initiation of XTANDI. Patients experiencing seizure were permanently discontinued from therapy, and all seizure events resolved.

In a single-arm trial designed to assess the risk of seizure in patients with pre-disposing factors for seizure, 8 of 366 (2.2%) XTANDI-treated patients experienced a seizure. Three of the 8 patients experienced a second seizure during continued treatment with XTANDI after their first seizure resolved. It is unknown whether anti-epileptic medications will prevent seizures with XTANDI. Patients in the study had one or more of the following pre-disposing factors: the use of medications that may lower the seizure threshold (~ 54%), history of traumatic brain or head injury (~ 28%), history of cerebrovascular accident or transient ischemic attack (~ 24%), and Alzheimer's disease, meningioma, or leptomeningeal disease from prostate cancer, unexplained loss of consciousness within the last 12 months, past history of seizure, presence of a space occupying lesion of the brain, history of arteriovenous malformation, or history of brain infection (all < 5%). Approximately 17% of patients had more than one risk factor.

Advise patients of the risk of developing a seizure while receiving XTANDI and of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others.

Permanently discontinue XTANDI in patients who develop a seizure during treatment.

Posterior Reversible Encephalopathy Syndrome (PRES)

There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving XTANDI. PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinue XTANDI in patients who develop PRES.

Hypersensitivity

Hypersensitivity reactions, including edema of the face (0.5%), tongue (0.1%), or lip (0.1%) have been observed with enzalutamide in eight randomized clinical trials. Pharyngeal edema has been reported in post-marketing cases. Advise patients who experience any symptoms of hypersensitivity to temporarily discontinue XTANDI and promptly seek medical care. Permanently discontinue XTANDI for serious hypersensitivity reactions.

Ischemic Heart Disease

In the combined data of five randomized, placebo-controlled clinical studies, ischemic heart disease occurred more commonly in patients on the XTANDI arm compared to patients on the placebo arm (3.5% vs 2%). Grade 3-4 ischemic events occurred in 1.8% of patients on the XTANDI arm compared to 1.1% on the placebo arm. Ischemic events led to death in 0.4% of patients on the XTANDI arm compared to 0.1% on the placebo arm.

Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue XTANDI for Grade 3-4 ischemic heart disease.

Falls and Fractures

Falls and fractures occurred in patients receiving XTANDI. Evaluate patients for fracture and fall risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

In the combined data of five randomized, placebo-controlled clinical studies, falls occurred in 12% of patients treated with XTANDI compared to 6% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Fractures occurred in 13% of patients treated with XTANDI and in 6% of patients treated with placebo. Grade 3-4 fractures occurred in 3.4% of patients treated with XTANDI and in 1.9% of patients treated with placebo. The median time to onset of fracture was 420 days (range: 1 to 2348 days) for patients treated with XTANDI. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the studies.

Embryo-Fetal Toxicity

The safety and efficacy of XTANDI have not been established in females. Based on animal reproductive studies and mechanism of action, XTANDI can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment with XTANDI and for 3 months after the last dose of XTANDI.

ADVERSE REACTIONS

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.

The data in WARNINGS and PRECAUTIONS reflect eight randomized, controlled trials [AFFIRM, PREVAIL, TERRAIN, PROSPER, ARCHES, EMBARK, Asian PREVAIL (NCT02294461), and STRIVE (NCT01664923)] that were pooled to conduct safety analyses in patients with CRPC (N = 3651), mCSPC (N = 752), or nmCSPC with high-risk BCR (N = 707) treated with XTANDI. Patients received XTANDI 160 mg (N = 5110) or placebo orally once daily (N = 2829) or bicalutamide 50 mg orally once daily (N = 387). In these eight trials, the median duration of treatment was 22.1 months (range: < 0.1 to 95.0) in patients that received XTANDI.

In five placebo-controlled trials (AFFIRM, PROSPER, PREVAIL, ARCHES, and EMBARK), the median duration of treatment was 19.4 months (range: < 0.1 to 90.4) in the XTANDI group. In these five trials, the most common adverse reactions (≥ 10%) that occurred more frequently (≥ 2% over placebo) in the XTANDI-treated patients were musculoskeletal pain, fatigue, hot flush, constipation, decreased appetite, diarrhea, hypertension, hemorrhage, fall, fracture, and headache.

AFFIRM: XTANDI versus Placebo in Metastatic CRPC Following Chemotherapy

AFFIRM enrolled 1199 patients with metastatic CRPC who had previously received docetaxel. The median duration of treatment was 8.3 months with XTANDI and 3.0 months with placebo. During the trial, 48% of patients on the XTANDI arm and 46% of patients on the placebo arm received glucocorticoids.

Grade 3 and higher adverse reactions were reported among 47% of XTANDI-treated patients. Discontinuations due to adverse reactions were reported for 16% of XTANDI-treated patients. The most common adverse reaction leading to treatment discontinuation was seizure, which occurred in 0.9% of the XTANDI-treated patients compared to none (0%) of the placebo-treated patients. Table 1 shows adverse reactions reported in AFFIRM that occurred at a ≥ 2% higher frequency in the XTANDI arm compared to the placebo arm.

Table 1. Adverse Reactions in AFFIRM

	XTANDI (N = 800)		Placebo (N = 399)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
General Disorders				
Asthenic Conditions[2]	51	9	44	9
Peripheral Edema	15	1	13	0.8
Musculoskeletal and Connective Tissue Disorders				
Back Pain	26	5	24	4
Arthralgia	21	2.5	17	1.8
Musculoskeletal Pain	15	1.3	12	0.3
Muscular Weakness	10	1.5	7	1.8
Musculoskeletal Stiffness	2.6	0.3	0.3	0
Gastrointestinal Disorders				
Diarrhea	22	1.1	18	0.3
Vascular Disorders				
Hot Flush	20	0	10	0
Hypertension	6	2.1	2.8	1.3
Nervous System Disorders				
Headache	12	0.9	5	0
Dizziness[3]	9	0.5	7	0.5
Spinal Cord Compression and Cauda Equina Syndrome	7	7	4.5	3.8
Paresthesia	7	0	4.5	0
Mental Impairment Disorders[4]	4.3	0.3	1.8	0
Hypoesthesia	4	0.3	1.8	0

Table 1. Adverse Reactions in AFFIRM (cont'd)

	XTANDI (N = 800)		Placebo (N = 399)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Infections and Infestations				
Upper Respiratory Tract Infection[5]	11	0	6	0.3
Lower Respiratory Tract And Lung Infection[6]	8	2.4	4.8	1.3
Psychiatric Disorders				
Insomnia	9	0	6	0.5
Anxiety	6	0.3	4	0
Renal and Urinary Disorders				
Hematuria	7	1.8	4.5	1
Pollakiuria	4.8	0	2.5	0
Injury, Poisoning and Procedural Complications				
Fall	4.6	0.3	1.3	0
Non-pathologic Fractures	4	1.4	0.8	0.3
Skin and Subcutaneous Tissue Disorders				
Pruritus	3.8	0	1.3	0
Dry Skin	3.5	0	1.3	0
Respiratory Disorders				
Epistaxis	3.3	0.1	1.3	0.3

1. CTCAE v 4.
2. Includes asthenia and fatigue.
3. Includes dizziness and vertigo.
4. Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention.
5. Includes nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis.
6. Includes pneumonia, lower respiratory tract infection, bronchitis, and lung infection.

PREVAIL: XTANDI versus Placebo in Chemotherapy-naïve Metastatic CRPC

PREVAIL enrolled 1717 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 1715 received at least one dose of study drug. The median duration of treatment was 17.5 months with XTANDI and 4.6 months with placebo. Grade 3-4 adverse reactions were reported in 44% of XTANDI-treated patients and 37% of placebo-treated patients. Discontinuations due to adverse reactions were reported for 6% of XTANDI-treated patients. The most common adverse reaction leading to treatment discontinuation was fatigue/asthenia, which occurred in 1% of patients on each treatment arm. Table 2 includes adverse reactions reported in PREVAIL that occurred at a ≥ 2% higher frequency in the XTANDI arm compared to the placebo arm.

Table 2. Adverse Reactions in PREVAIL

	XTANDI (N = 871)		Placebo (N = 844)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
General Disorders				
Asthenic Conditions[2]	47	3.4	33	2.8
Peripheral Edema	12	0.2	8	0.4
Musculoskeletal and Connective Tissue Disorders				
Back Pain	29	2	22	3
Arthralgia	21	1.6	16	1.1
Gastrointestinal Disorders				
Constipation	23	0.7	17	0.4
Diarrhea	17	0.3	14	0.4
Vascular Disorders				
Hot Flush	18	0.1	8	0
Hypertension	14	7	4.1	2.3
Nervous System Disorders				
Dizziness[3]	11	0.3	7	0
Headache	11	0.2	7	0.4
Dysgeusia	8	0.1	3.7	0
Mental Impairment Disorders[4]	6	0	1.3	0.1
Restless Legs Syndrome	2.1	0.1	0.4	0
Respiratory Disorders				
Dyspnea[5]	11	0.6	8	0.6
Infections and Infestations				
Upper Respiratory Tract Infection[6]	16	0	11	0
Lower Respiratory Tract And Lung Infection[7]	8	1.5	4.7	1.1
Psychiatric Disorders				
Insomnia	8	0.1	6	0
Renal and Urinary Disorders				
Hematuria	9	1.3	6	1.3
Injury, Poisoning and Procedural Complications				
Fall	13	1.6	5	0.7
Non-Pathological Fracture	9	2.1	3	1.1
Metabolism and Nutrition Disorders				
Decreased Appetite	19	0.3	16	0.7
Investigations				
Weight Decreased	12	0.8	8	0.2
Reproductive System and Breast Disorders				
Gynecomastia	3.4	0	1.4	0

1. CTCAE v 4.
2. Includes asthenia and fatigue.
3. Includes dizziness and vertigo.
4. Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention.
5. Includes dyspnea, exertional dyspnea, and dyspnea at rest.
6. Includes nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis.
7. Includes pneumonia, lower respiratory tract infection, bronchitis, and lung infection.

TERRAIN: XTANDI versus Bicalutamide in Chemotherapy-naïve Metastatic CRPC

TERRAIN enrolled 375 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 372 received at least one dose of study drug. The median duration of treatment was 11.6 months with XTANDI and 5.8 months with bicalutamide. Discontinuations with an adverse reaction as the primary reason were reported for 8% of XTANDI-treated patients and 6% of bicalutamide-treated patients. The most common adverse reactions leading to treatment discontinuation were back pain and pathological fracture, which occurred in 3.8% of XTANDI-treated patients for each event and in 2.1% and 1.6% of bicalutamide-treated patients, respectively. Table 3 shows overall and common adverse reactions (≥ 10%) in XTANDI-treated patients.

Table 3. Adverse Reactions in TERRAIN

	XTANDI (N = 183)		Bicalutamide (N = 189)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Overall	94	39	94	38
General Disorders				
Asthenic Conditions[2]	32	1.6	23	1.1
Musculoskeletal and Connective Tissue Disorders				
Back Pain	19	2.7	18	1.6
Musculoskeletal Pain[3]	16	1.1	14	0.5
Vascular Disorders				
Hot Flush	15	0	11	0
Hypertension	14	7	7	4.2
Gastrointestinal Disorders				
Nausea	14	0	18	0
Constipation	13	1.1	13	0.5
Diarrhea	12	0	9	1.1
Infections and Infestations				
Upper Respiratory Tract Infection[4]	12	0	6	0.5
Investigational				
Weight Loss	11	0.5	8	0.5

1. CTCAE v 4.
2. Includes asthenia and fatigue.
3. Includes musculoskeletal pain and pain in extremity.
4. Includes nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis.

PROSPER: XTANDI versus Placebo in Non-metastatic CRPC Patients

PROSPER enrolled 1401 patients with non-metastatic CRPC, of whom 1395 received at least one dose of study drug. Patients were randomized 2:1 and received either XTANDI at a dose of 160 mg once daily (N = 930) or placebo (N = 465). The median duration of treatment at the time of analysis was 18.4 months (range: 0.0 to 42 months) with XTANDI and 11.1 months (range: 0.0 to 43 months) with placebo.

Overall, 32 patients (3.4%) receiving XTANDI died from adverse reactions. The reasons for death with ≥ 2 patients included coronary artery disorders (n = 7), sudden death (n = 2), cardiac arrhythmias (n = 2), general physical health deterioration (n = 2), stroke (n = 2), and secondary malignancy (n = 5; one each of acute myeloid leukemia, brain neoplasm, mesothelioma, small cell lung cancer, and malignant neoplasm of unknown primary site). Three patients (0.6%) receiving placebo died from adverse reactions of cardiac arrest (n = 1), left ventricular failure (n = 1), and pancreatic carcinoma (n = 1). Grade 3 or higher adverse reactions were reported among 31% of XTANDI-treated patients and 23% of placebo-treated patients. Discontinuations with an adverse reaction as the primary reason were reported for 9% of XTANDI-treated patients and 6% of placebo-treated patients. Of these, the most common adverse reaction leading to treatment discontinuation was fatigue, which occurred in 1.6% of the XTANDI-treated patients compared to none of the placebo-treated patients. Table 4 shows adverse reactions reported in PROSPER that occurred at a ≥ 2% higher frequency in the XTANDI arm than in the placebo arm.

Table 4. Adverse Reactions in PROSPER

	XTANDI (N = 930)		Placebo (N = 465)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Metabolism and Nutrition Disorders				
Decreased Appetite	10	0.2	3.9	0.2
Nervous System Disorders				
Dizziness[2]	12	0.5	5	0
Headache	9	0.2	4.5	0
Cognitive And Attention Disorders[3]	4.6	0.1	1.5	0
Vascular Disorders				
Hot Flush	13	0.1	8	0
Hypertension	12	4.6	5	2.2
Gastrointestinal Disorders				
Nausea	11	0.3	9	0
Constipation	9	0.2	7	0.4
General Disorders and Administration Site Conditions				
Asthenic Conditions[4]	40	4	20	0.9
Investigations				
Weight Decreased	6	0.2	1.5	0
Injury, Poisoning and Procedural Complications				
Fall	11	1.3	4.1	0.6
Fractures[5]	10	2	4.9	1.7
Psychiatric Disorders				
Anxiety	2.8	0.2	0.4	0

1. CTCAE v 4.
2. Includes dizziness and vertigo.
3. Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention.
4. Includes asthenia and fatigue.
5. Includes all osseous fractures from all sites.

ARCHES: XTANDI versus Placebo in Metastatic CSPC Patients

ARCHES randomized 1150 patients with mCSPC, of whom 1146 received at least one dose of study drug. All patients received either a gonadotropin-releasing hormone (GnRH) analog concurrently or had bilateral orchiectomy. Patients received either XTANDI at a dose of 160 mg once daily (N = 572) or placebo (N = 574). The median duration of treatment was 12.8 months (range: 0.2 to 26.6 months) with XTANDI and 11.6 months (range: 0.2 to 24.6 months) with placebo. Overall, 10 patients (1.7%) receiving XTANDI died from adverse reactions. The reasons for death in ≥ 2 patients included heart disease (n = 3), sepsis (n = 2) and pulmonary embolism (n = 2). Eight patients (1.4%) receiving placebo died from adverse reactions. The reasons for death in ≥ 2 patients included heart disease (n = 2) and sudden death (n = 2). Grade 3 or higher adverse reactions were reported in 24% of patients treated with XTANDI. Permanent discontinuation due to adverse reactions as the primary reason was reported in 4.9% of XTANDI-treated patients and 3.7% of placebo-treated patients. The most common adverse reactions resulting in permanent discontinuation in XTANDI-treated patients were alanine aminotransferase increased, aspartate aminotransferase elevation, and seizure, each in 0.3%. The most common adverse reactions leading to permanent discontinuation in placebo-treated patients were arthralgia, and fatigue, each in 0.3%. Dose reductions due to an adverse reaction occurred in 4.4% of patients who received XTANDI. Fatigue/asthenia was the most frequent adverse reaction requiring dose reduction in 2.1% of XTANDI-treated patients and 0.7% of placebo-treated patients. Table 5 shows adverse reactions reported in ARCHES that occurred at a ≥ 2% higher frequency in the XTANDI arm than in the placebo arm.

Table 5. Adverse Reactions in ARCHES

	XTANDI (N = 572)		Placebo (N = 574)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Metabolism and Nutrition Disorders				
Decreased Appetite	4.9	0.2	2.6	0
Nervous System Disorders				
Cognitive and Memory Impairment[2]	4.5	0.7	2.1	0
Restless Legs Syndrome	2.4	0	0.3	0
Vascular Disorders				
Hot Flush	27	0.3	22	0
Hypertension	8	3.3	6	1.7
General Disorders and Administration Site Conditions				
Asthenic conditions[3]	24	1.7	20	1.6
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain	6	0.2	4	0.2
Injury, Poisoning and Procedural Complications				
Fractures[4]	6	1	4.2	1

1. CTCAE v 4.03.
2. Includes memory impairment, amnesia, cognitive disorder, dementia, disturbance in attention, transient global amnesia, dementia alzheimer's type, mental impairment, senile dementia and vascular dementia.
3. Includes asthenia and fatigue.
4. Includes Fracture related preferred terms under high level terms: fractures NEC; fractures and dislocations NEC; limb fractures and dislocations; pelvic fractures and dislocations; skull and brain therapeutic procedures; skull fractures, facial bone fractures and dislocations; spinal fractures and dislocations; thoracic cage fractures and dislocations.

EMBARK: XTANDI versus Placebo in Nonmetastatic CSPC Patients with High-risk BCR

EMBARK enrolled 1068 patients with high-risk BCR, of whom 1061 patients received at least one dose of study drug. Patients received XTANDI at a dose of 160 mg once daily concurrently with leuprolide (N = 353), XTANDI at a dose of 160 mg once daily as open-label monotherapy (N = 354), or placebo concurrently with leuprolide (N = 354). At week 37, treatment was suspended for patients whose PSA values were undetectable (< 0.2 ng/mL) at week 36. Treatment was reinitiated when PSA values increased to ≥ 2.0 ng/mL for patients with prior prostatectomy or ≥ 5.0 ng/mL for patients without prior prostatectomy. For patients whose PSA values were detectable (≥ 0.2 ng/mL) at week 36, treatment continued without suspension until permanent treatment discontinuation criteria were met. Table 6 shows the total duration of treatment for the three treatment arms.

Table 6. Drug Treatment and Suspension in EMBARK

	XTANDI + Leuprolide (N = 353)	Placebo + Leuprolide (N = 354)	XTANDI (N = 354)
Total Duration of Treatment[1]			
Median, months	60.6	55.6	60.4
Range, months	0.1 – 90.4	0.7 – 94.1	0.4 – 95.0
Duration Receiving Drug Treatment			
Median, months	32.4	35.4	45.9
Range, months	0.1 – 83.4	0.7 – 85.7	0.4 – 88.9
Duration of Suspension from Drug Treatment			
Median, months	20.2	16.8	11.1
Range, months	5.7 – 87.9	3.4 – 83.0	2.3 – 84.9
Patients who had Drug Treatment Suspended at Week 37			
Number of Patients (%)	321 (90.9)	240 (67.8)	304 (85.9)

1. Inclusive of time receiving drug treatment plus any time during which drug treatment was suspended because of undetectable PSA levels.

Overall, deaths from adverse reactions during the total duration of treatment occurred in 6 patients (1.7%) receiving XTANDI plus leuprolide, 8 patients (2.3%) receiving XTANDI as a single agent, and 3 patients (0.8%) receiving placebo plus leuprolide. The reason for death in ≥ 2 patients receiving XTANDI plus leuprolide was infection (n = 2), and the reason for death in ≥ 2 patients receiving XTANDI as a single agent was arterial thromboembolism (n = 2). Grade 3 or higher adverse reactions during the total duration of treatment were reported in 46% of patients treated with XTANDI plus leuprolide, 50% of patients receiving XTANDI as a single agent, and 43% of patients receiving placebo plus leuprolide. Permanent treatment discontinuation due to adverse reactions during the total duration of treatment as the primary reason was reported in 21% of patients treated with XTANDI plus leuprolide, 18% of patients receiving XTANDI as a single agent, and 10% of patients receiving placebo plus leuprolide. The most common adverse reactions resulting in permanent discontinuation included fatigue (3.4% of patients treated with XTANDI plus leuprolide, 3.7% of patients receiving XTANDI as a single agent, and 1.4% of patients receiving placebo plus leuprolide), hot flush (2% of patients treated with XTANDI plus leuprolide, 0% of patients receiving XTANDI as a single agent, and 1.1% of patients receiving placebo plus leuprolide), nausea (1.1% of patients treated with XTANDI plus leuprolide, 0.6% of patients receiving XTANDI as a single agent, and 0.3% of patients receiving placebo plus leuprolide), and cognitive disorder (1.1% of patients treated with XTANDI plus leuprolide, 1.4% of patients receiving XTANDI as a single agent, and 0.8% of patients receiving placebo plus leuprolide).

Dose reductions due to an adverse reaction occurred in 7% of patients who received XTANDI plus leuprolide, 16% of patients who received XTANDI as a single agent, and 4.5% of patients who received placebo plus leuprolide. Fatigue was the most frequent adverse reaction requiring dose reduction in 3.1% of patients treated with XTANDI plus leuprolide, 10% of patients receiving XTANDI as a single agent, and 1.7% of patients receiving placebo plus leuprolide.

Table 7 shows adverse reactions reported in EMBARK that occurred at a ≥ 5% (Grade 1-4) or ≥ 2% (Grade 3-4) higher frequency in either of the XTANDI arms than in the placebo arm.

Table 7. Adverse Reactions in EMBARK

	XTANDI + Leuprolide (N = 353)		Placebo + Leuprolide (N = 354)		XTANDI (N = 354)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Nervous System Disorders						
Cognitive Disorder[2]	10	0.3	4.8	0.6	10	0.3
Syncope	4.8	4.2	2.3	1.7	2.5	2
Vascular Disorders						
Hot Flush	69	0.6	57	0.8	22	0.3
Hemorrhage[2]	20	3.4	15	1.7	21	3.7
Gastrointestinal Disorders						
Diarrhea[2]	15	0.6	9	0.8	14	0.3
Nausea	12	0.3	8	0.3	15	0.6
Investigations						
Weight Decreased	7	0.3	3.4	0	11	0.3
General Disorders and Administration Site Conditions						
Fatigue[2]	50	4	38	1.7	54	4.8
Musculoskeletal and Connective Tissue Disorders						
Musculoskeletal Pain[2]	50	4.8	43	2.3	48	3.1
Osteoarthritis	6	2.8	4.2	0.6	5	0.6
Injury, Poisoning and Procedural Complications						
Fall	21	1.1	14	1.1	16	2
Fracture[2]	18	4	13	2.5	11	2
Reproductive System and Breast Disorders						
Gynecomastia[2]	9	0	10	0	49	0.8
Breast Tenderness[2]	5	0	2.8	0	35	0
Cardiac Disorders						
Ischemic Heart Disease[2]	5	4	6	3.1	9	6

1. CTCAE v 4.03.
2. Includes multiple terms.

Laboratory Abnormalities

Table 8 shows laboratory abnormalities that occurred in ≥ 5% of patients, and more frequently (> 2%) in the XTANDI arm compared to placebo in the pooled, randomized, placebo-controlled studies.

Table 8. Laboratory Abnormalities

	XTANDI (N = 3526)		Placebo (N = 2636)	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Hematology				
Hemoglobin decreased	50	1.8	47	1.5
Neutrophil count decreased	20	1	17	0.5
White blood cell decreased	18	0.5	11	0.2
Chemistry				
Hyperglycemia	86	3.7	78	4.3
Hypermagnesemia	17	0.1	14	0.3
Hyponatremia	14	1.6	9	1.4
Hypophosphatemia	10	1.4	7	0.8
Hypercalcemia	8	0.1	5	0.1

Hypertension

In the combined data from five randomized placebo-controlled clinical trials, hypertension was reported in 14% of patients receiving XTANDI and 7% of patients receiving placebo. Medical history of hypertension was balanced between arms. Hypertension led to study discontinuation in < 1% of patients in each arm.

Post-Marketing Experience

The following additional adverse reactions have been identified during post-approval use of XTANDI. 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.

Gastrointestinal Disorders: vomiting
Immune System Disorders: hypersensitivity (edema of the face, tongue, lip, or pharynx)
Neurological Disorders: posterior reversible encephalopathy syndrome (PRES), dysgeusia
Skin and Subcutaneous Tissue Disorders: rash, severe cutaneous adverse reactions (including Stevens-Johnson syndrome (SJS), erythema multiforme, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP))

DRUG INTERACTIONS

Effect of Other Drugs on XTANDI

Strong CYP2C8 Inhibitors

The coadministration of XTANDI with gemfibrozil (a strong CYP2C8 inhibitor) increases plasma concentrations of enzalutamide plus N-desmethyl enzalutamide, which may increase the incidence and severity of adverse reactions of XTANDI. Avoid the coadministration of XTANDI with strong CYP2C8 inhibitors. If the coadministration of XTANDI with a strong CYP2C8 inhibitor cannot be avoided, reduce the dosage of XTANDI.

Strong CYP3A4 Inducers

The coadministration of XTANDI with rifampin (a strong CYP3A4 inducer and a moderate CYP2C8 inducer) decreases plasma concentrations of enzalutamide plus N-desmethyl enzalutamide, which may decrease the efficacy of XTANDI. Avoid the coadministration of XTANDI with a strong CYP3A4 inducer with strong CYP3A4 inducers. If the coadministration of XTANDI cannot be avoided, increase the dosage of XTANDI.

Effect of XTANDI on Other Drugs

Certain CYP3A4, CYP2C9, or CYP2C19 Substrates

XTANDI is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer. The coadministration of XTANDI decreases the concentrations of certain CYP3A4, CYP2C9, or CYP2C19 substrates, which may reduce the efficacy of these substrates. Avoid the coadministration of XTANDI with certain CYP3A4, CYP2C9, or CYP2C19 substrates for which a minimal decrease in concentration may lead to therapeutic failure of the substrate. If the coadministration cannot be avoided, increase the dosage of these substrates in accordance with their Prescribing Information. In cases where active metabolites are formed, there may be increased exposure to the active metabolites.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

The safety and efficacy of XTANDI have not been established in females. Based on animal reproductive studies and mechanism of action, XTANDI can cause fetal harm and loss of pregnancy. There are no human data on the use of XTANDI in pregnant females. In animal reproduction studies, oral administration of enzalutamide in pregnant mice during organogenesis caused adverse developmental effects at doses lower than the maximum recommended human dose *(see Data)*.

Data

Animal Data
In an embryo-fetal developmental toxicity study in mice, enzalutamide caused developmental toxicity when administered at oral doses of 10 or 30 mg/kg/day throughout the period of organogenesis (gestational days 6-15). Findings included embryo-fetal lethality (increased post-implantation loss and resorptions) and decreased anogenital distance at ≥ 10 mg/kg/day, and cleft palate and absent palatine bone at 30 mg/kg/day. Doses of 30 mg/kg/day caused maternal toxicity. The doses tested in mice (1, 10 and 30 mg/kg/day) resulted in systemic exposures (AUC) approximately 0.04, 0.4 and 1.1 times, respectively, the exposures in patients. Enzalutamide did not cause developmental toxicity in rabbits when administered throughout the period of organogenesis (gestational days 6-18) at dose levels up to 10 mg/kg/day (approximately 0.4 times the exposures in patients based on AUC).

In a pharmacokinetic study in pregnant rats with a single oral 30 mg/kg enzalutamide administration on gestation day 14, enzalutamide and/or its metabolites were present in the fetus at a C_{max} that was approximately 0.3 times the concentration found in maternal plasma and occurred 4 hours after administration.

Lactation

Risk Summary

The safety and efficacy of XTANDI have not been established in females. There is no information available on the presence of XTANDI in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Enzalutamide and/or its metabolites were present in milk of lactating rats *(see Data)*.

Data

Following a single oral administration in lactating rats on postnatal day 14, enzalutamide and/or its metabolites were present in milk at a C_{max} that was 4 times higher than concentrations in the plasma and occurred 4 hours after administration.

Females and Males of Reproductive Potential

Contraception

Males
Based on findings in animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of XTANDI.

Infertility

Males

Based on animal studies, XTANDI may impair fertility in males of reproductive potential.

Pediatric Use

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

Geriatric Use

Of 5110 patients who received XTANDI in eight randomized, controlled clinical trials, 78% were 65 and over, while 33% were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Renal Impairment

No dosage modification is recommended for patients with mild to moderate renal impairment (creatinine clearance [CLcr] ≥ 30 mL/min). XTANDI has not been studied in patients with severe renal impairment (CLcr < 30 mL/min) or end-stage renal disease.

Hepatic Impairment

No dosage modification is recommended for patients with mild, moderate, or severe hepatic impairment.

OVERDOSAGE

In the event of an overdosage, stop treatment with XTANDI and initiate general supportive measures taking into consideration the half-life of 5.8 days. In a dose escalation study, no seizures were reported at ≤ 240 mg daily, whereas 3 seizures were reported, 1 each at 360 mg, 480 mg, and 600 mg daily. Patients may be at increased risk of seizure following an overdosage.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

A two-year carcinogenicity study was conducted in male and female rats at oral enzalutamide doses of 10, 30, and 100 mg/kg/day. Enzalutamide increased the incidence of benign Leydig cell tumors in the testes at all dose levels tested (≥ 0.3 times the human exposure based on AUC) and combined incidence of urothelial papilloma and carcinoma in the urinary bladder in male rats at 100 mg/kg/day (1.4 times the human exposure based on AUC). The findings in the testes are considered to be related to the pharmacological activity of enzalutamide. Rats are regarded as more sensitive than humans to developing interstitial cell tumors in the testes. Administration of enzalutamide to male and female rasH2 transgenic mice by oral gavage daily for 26 weeks did not result in increased incidence of neoplasms at doses up to 20 mg/kg/day.

Enzalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either the *in vitro* mouse lymphoma thymidine kinase (Tk) gene mutation assay or the *in vivo* mouse micronucleus assay.

Based on nonclinical findings in repeat-dose toxicology studies, which were consistent with the pharmacological activity of enzalutamide, male fertility may be impaired by treatment with XTANDI. In a 26-week study in rats, atrophy of the prostate and seminal vesicles was observed at ≥ 30 mg/kg/day (equal to the human exposure based on AUC). In 4-, 13-, and 39-week studies in dogs, hypospermatogenesis and atrophy of the prostate and epididymides were observed at ≥ 4 mg/kg/day (0.3 times the human exposure based on AUC).

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AUA2024 PREVIEW

Prevention and Treatment of Inflatable Penile Prosthesis Infection, and Placement Following Explant

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Implantation of a penile prosthesis for treatment of erectile dysfunction has been around for almost 100 years. The inflatable penile prosthesis was introduced 50 years ago. It has been estimated that somewhere between 20,000 and 25,000 of these devices are implanted annually in the US. A penile prosthesis remains one of the most successful ways to treat advanced erectile dysfunction, particularly when oral therapy, injection therapy, or vacuum therapy are found not to provide satisfactory rigidity or when they are not acceptable to the patient. Patient and partner satisfaction rates remain high.[1,2] But as with any surgery, there are potential complications. The most dreaded complication with any implant is infection, as it invariably means the device has to be removed. Explant of an infected penile prosthesis causes significant distress for the patient and his partner, but also creates significant stress on the medical system as well as a financial burden.[3] Therefore, efforts to reduce prosthesis infection have been pursued over the past 4 to 5 decades. Infection rates currently with the initial placement of a 3-piece prosthesis are typically reported in the 1% to 3% range.[4] But it was not long ago when these rates were substantially higher, before infection-retardant coatings were introduced.[5,6] A variety of infection control approaches have been suggested in a penile prosthesis checklist, which includes pre-, intra-, and postoperative measures that are recommended to reduce the risk of infection.[7] In addition, properly selected preoperative antibiotics have likely also reduced infection rates and are now included in medical society guidelines worldwide.[8-10] We have also learned that revision of a noninfected penile prosthesis is associated with a higher infection rate, likely due to activation of quiescent bacteria on the surface of the prosthesis, and that intraoperative irrigation with antibiotics, antifungals, and antiseptics can reduce postoperative infection in this population as well.[11] There are also certain patient populations who may be at higher risk for infection including uncontrolled diabetics, immunosuppressed individuals, and others who are prone to UTI such as those with neurogenic bladder.[12]

This session of the Plenary Second Opinion Panel will review several topics associated with penile prosthesis infection. First, Dr Lawrence Hakim, chairman of urology at Cleveland Clinic Florida, will review the evidence behind pre- and perioperative techniques to reduce the risk of infection. The second topic will be addressed by Dr John Mulcahy, professor of urology at the University of Alabama, who introduced the major breakthrough of immediate salvage of the infected prosthesis using a combination of different solutions to irrigate the field.[13] Immediate salvage has been shown to be useful as it prevents corporal fibrosis, preserves penile length, avoids subsequent staged reimplant, and accelerates return to sexual activity. Dr Mulcahy will review how the salvage procedure has evolved over the past 25 years to using different antibiotic and antiseptic solutions based upon reduced toxicity and better coverage for the most frequent organisms found today.[13,14] Most recently, immediate salvage has had a reported success rate of 93%.[15] Salvaging with a malleable implant has emerged as the preferred approach as compared to a 3-piece inflatable device, as it reduces operation time, avoids a scrotal and reservoir component, and preserves penile space should a switch-out to an inflatable device be desired at a later time (usually >3 months to allow full healing).[16,17] Historically, the contraindications to immediate salvage included local soft tissue necrosis, device erosion, diabetic ketoacidosis, sepsis, significant purulence, immunosuppression, or urethral injury. As a result of the advancements in this field, many more of these patients may now be candidates for immediate salvage. Interestingly, one would think that most men would be offered immediate salvage with the reported success rate, but in a review of national trends 10 years ago, only 17.3% did undergo this procedure.[18]

Finally, Dr Ricardo Munarriz, professor of urology at Boston University Medical Center, will review techniques to optimize delayed replacement of a penile prosthesis following explantation of an infected penile prosthesis. This can be a rather complex surgical procedure due to severe corporal fibrosis. Techniques have emerged that have facilitated placement of a new full-size prosthesis, such as several months of daily vacuum therapy, but when severe corporal fibrosis persists a variety of techniques may be needed by the surgeon including extended or multiple corporotomies, use of cavernotomes, or even full corporal scar excavation to be able to place a full-size or narrow-base prosthesis.[19,20]

The key is penile prostheses remain a critically important and successful modality to restore the ability of a man to have a rigid penis on demand without compromising sensation, orgasm, ejaculation, and urination. It is usually a straightforward and simple operation, typically performed today as an outpatient, but can also be a complex operation requiring advanced surgical skills, particularly when an infection develops or there is a fibrotic corpus cavernosum. Clearly prevention of infection is of the utmost importance at the time of prosthesis placement. ■

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AUA2024 PREVIEW

Dyspareunia: From Concept to Care

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Dyspareunia is the term used to describe genitopelvic pain that is provoked by sexual activity. It is a sexual problem, a diagnosis that merits treatment, but it is also the norm for women insofar as normality is defined in statistical terms. Studies have shown that 3 out of 4 women report having experienced dyspareunia at least once, and between 10% and 20% of women experience it chronically.[1] Men may also experience it, as 1% to 5% of men also report pain with sexual intercourse, but these numbers are low enough to be unambiguous in their abnormality.[2] In contrast, women are taught to expect sex to be physically painful, at least at first, and that expectation, normalization, and encouragement to tolerate coital pain remains a persistent theme in female sexual education.

Dyspareunia is often assumed to be due to penetrative intercourse and to be a gendered phenomenon caused by penovaginal penetration and experienced exclusively by the penetrated female partner. This assumption is reflected in the International Classification of Diseases and Diagnostic and Statistical Manual of Mental Disorders coding systems, both of which place the symptom dyspareunia under the diagnosis of genitopelvic pain–penetration disorder, a hyphenated condition that is gendered female. By design, this system neglects the pain of men who prefer receptive anal intercourse, men who experience pain with orgasm whether they are acting as top or bottom, and the pain women may experience by genital contact in the absence of penetration, which tends to be even more debilitating than vaginismus as it occurs in both erotic and nonsexual contexts.

How we conceptualize pain and define dyspareunia are foundational to accurate diagnosis across the various populations who experience it and to effective therapy. As biomedical knowledge has evolved over time, so has our understanding of pain: it is variously understood as a response to an aversive physical stimulus or tissue pathology, a peripheral neurologic phenomenon that can be mapped onto specific nerve routes, or a somatosensory psychological experience. This last conceptualization de-emphasizes peripheral pathophysiology in favor of focusing on its central nervous and especially supratentorial, cognitive, and emotional aspects. These different ways of thinking about pain and its causes are represented in our current understanding of dyspareunia, its causes, and their best treatments.

For example, considering dyspareunia as a response to an aversive genital stimulus encourages us to examine the affected area with more thoughtful care in order to seek, find, and eliminate the underlying cause. A recent paper in *JAMA Dermatology* described treatment of chronic dyspareunia in a male patient by excision of a glanular pilonidal sinus, acquired due to ingrown hairs many years prior and identified on dermoscopy.[3] A similar phenomenon of dyspareunia in the setting of hairs, keratin pearls, smegma, and other debris trapped below the prepuce is often overlooked in women, whose genital examination conventionally ignores the clitoris. When these are addressed by lysis of adhesions and surgical repair of preputial phimosis, there can be significant improvement of pain and increased sexual pleasure.[4]

Often, the aversive stimulus causing pain is endogenous and hormone mediated, whether secondary to endometriosis, uterine fibroids, or genitourinary syndrome of menopause (GSM). This suggests that we treat the problem through hormone manipulation and other means of altering the diseased genital and pelvic parts. Conventionally, endometriosis and fibroids have been treated with surgical excision and attempts to suppress formation with oral contraceptive pills, though this is not always successful. Relugolix, a gonadotropin-releasing hormone antagonist familiar to urologists in the context of treatment for prostate cancer, is also Food and Drug Administration approved for treatment of pain due to endometriosis and uterine fibroids. Just as relugolix can cause symptoms of hypogonadism for the men who take it, its female parallel, relugolix/estradiol/norethisterone, and oral contraceptive pills can induce the symptoms and vulvovaginal atrophy characteristic of GSM. For women who are reluctant to treat GSM with estrogens, the PIVoT (Prevention of Recurrent Urinary Tract Infection Using Vaginal Testosterone) randomized controlled trial supports the use of topical vulvovaginal testosterone as an off-label alternative.[5]

For patients who wish to avoid hormonal treatments altogether, energy-based therapies are a compelling strategy that merits further research and exploration. However, the checkered track record of vaginal CO_2 lasers is a caution against too-early adoption of novel devices: only after they were widely advertised and invested in was it recognized that these devices may worsen vulvovaginal pain, rather than improve it.[6,7] Less risky, nontissue ablative interventions such as low-intensity shock wave[8] and photobiomodulation devices have all shown promise as research interventions for dyspareunia in women,[9] and the AUA guideline for Peyronie's disease endorses the use of shock wave therapy for painful erection, gesturing to its potential benefit for other forms of dyspareunia as well. While most research focuses these energies on the genitalia, some have shown reductions in dyspareunia with application of shock waves to the spinal nerve roots and near-infrared light to the brain.

The relationship of dyspareunia to the central nervous system, its conceptualization as a radiculopathy and/or a central nervous phenomenon, has been best elaborated on in the context of persistent genital arousal disorder, also known as genitopelvic dysesthesia. The International Society for the Study of Women's Sexual Health consensus paper mapping the genital pain of persistent genital arousal disorder onto 5 distinct but interactive regions within the body has relevance for other forms of dyspareunia as well, pointing to the promise of treatments that target areas outside the genitalia and true pelvis.[10] Orthopedic and neurosurgical interventions, physical therapy, as well as meditation and medications that target central sensitization to pain all show promise as treatments for dyspareunia, though the utility of any one of these will of course vary with specific patient phenotype and endotype. A thoughtful balance of both lumping and splitting, inclusive health care and precision medicine, is essential to the accurate diagnosis and treatment of dyspareunia. ■

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AUA2024 PREVIEW

How We Counsel Patients Regarding the Impact of COVID on Male Fertility

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Introduction

In December 2022, combined infection and vaccine-induced seroprevalence of COVID reached 98% of all US reproductive-aged adults. Additionally, the CDC estimates that 77.5% of the population has been infected at least once.[1] Given the ubiquitous nature of both exposure to and previous infection by the virus, its potential impact on fertility has been meticulously studied. Patients presenting for a reproductive health evaluation will commonly ask what the potential impact of COVID is on both their reproductive potential and chances of conception. Importantly, patients should be counseled that vaccination has no detrimental effects on fertility potential, while infection by the virus is known to have negative effects on both hormones and sperm production.[2,3] The virus has been found in both semen and the testis tissue, and its impact on testicular function and spermatogenesis are well described.[4] Patients should be counseled that COVID is not transmitted sexually, but standard precautions should be followed in the infected state.[5] COVID has been shown to induce orchitis, alter hormone levels, and affect sperm health acutely (Figure).

"Patients presenting for a reproductive health evaluation will commonly ask what the potential impact of COVID is on both their reproductive potential and chances of conception. Importantly, patients should be counseled that vaccination has no detrimental effects on fertility potential, while infection by the virus is known to have negative effects on both hormones and sperm production.[2,3]"

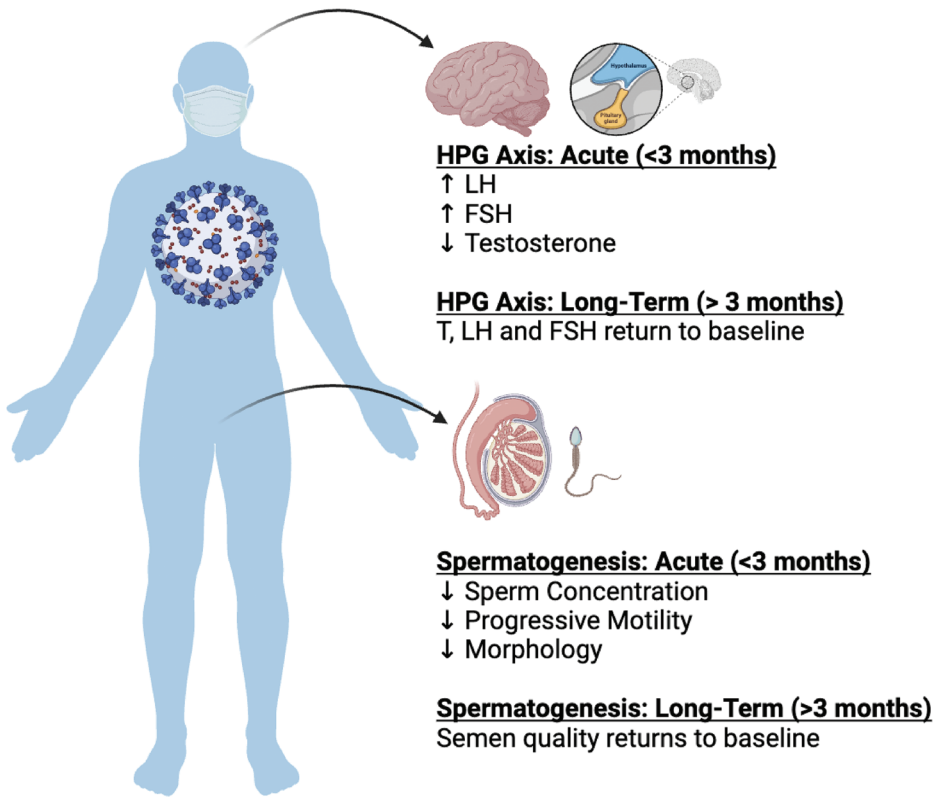

Figure. Effects of COVID infection on male fertility. FSH indicates follicle stimulating hormone; HPG, hypothalamic-pituitary-gonadal; LH, luteinizing hormone; T, testosterone. Created with BioRender.com.

Hormone Levels

In the acute setting, COVID infection has been shown to cause changes in the hypothalamic-pituitary-gonadal axis. Studies report that up to half of patients will have below normal serum testosterone levels during acute infection, with the lowest levels seen in patients with severe symptoms.[4,6] The etiology for this finding is likely secondary to decreased testicular function brought on by inflammation.[4] Additionally, these patients with acute infection concurrently had statistically significant increased luteinizing hormone and follicle stimulating hormone levels when compared with healthy controls.[4]

Of patients with decreased testosterone levels as a result of acute infection, most but not all return to normal testosterone levels at 3 months after infection.[4,6] Confounding this is the fact that men with persistent hypogonadism 12 months after infection may have been hypogonadal prior to infection.[4,6] Thus, patients exhibiting symptoms of hypogonadism even years out from infection should be evaluated and treated accordingly for this condition.

Spermatogenesis

Spermatogenesis is negatively affected by acute COVID infection. This is thought to be a result of fever, the inflammatory state brought about by infection, and dysregulation of the proteome in semen leading to spermatic dysfunction with regards to development, motility, and fertilization.[4] Donders et al report that up to 60% of patients will have decreased motility within 1 month after infection and 37% of patients will have decreased sperm counts.[2] Studies have shown a decrease in normal sperm morphology during the acute phase as well.[2] Patients should be counseled that initial negative impacts of COVID on spermatogenesis are temporary. Literature supports that decreases in semen parameters resolve at around 3 months after infection, or 1 spermatogenic cycle.[2,4]

The short-term nature of the effects of COVID on spermatogenesis is further supported in that patients who had a semen analysis prior to infection and after resolution of infection did not exhibit significantly different semen parameters.[4,7] Additionally, clinics have not seen an increase in the number of patients presenting with fertility issues nor the number of abnormal semen analysis results prepandemic vs present day.[7]

Conception and Pregnancy Outcomes

Females infected with COVID may have short-term hormonal, ovulatory, and menstrual irregularities as well.[4] However, in a large cohort study using the Pregnancy Study Online database, infection was not associated with significant decreases in female fecundability, while male fecundability was significantly decreased transiently.[8] Reassuringly, these authors did not

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HOW WE COUNSEL PATIENTS REGARDING THE IMPACT OF COVID ON MALE FERTILITY

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> "Donders et al report that up to 60% of patients will have decreased motility within 1 month after infection and 37% of patients will have decreased sperm counts.[2]"

find any persistence of decreased fecundability that extended beyond 60 days.[8]

For couples undergoing assisted reproductive techniques, history of COVID infection has not been shown to impact outcomes, including oocyte yield, fertilization and maturation rate, number of good quality embryos, and clinical pregnancy rates in fresh cycles.[9] Furthermore, the majority of studies report no change in outcomes for patients with previous infection undergoing frozen embryo transfers.[4] However, because of the known impact on spermatogenesis, reproductive endocrinologists may elect to delay assisted reproductive technique cycles in the event of male partner infection to allow spermatogenesis to recover.[4] The COVID vaccine has not been shown to negatively impact ovarian reserve or ovarian function.[4] Importantly, for couples who are already pregnant, exposure to the COVID vaccine in utero does not lead to an increased risk of spontaneous abortion.[10]

Infection with COVID does have acute effects on male fertility with both decreases in testosterone as well as decreased quality of sperm. Fortunately, these acute effects are reversed after resolution of acute infection for almost all patients. For those patients with persistent abnormalities postinfection, further workup into other potential etiologies should be performed. ■

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AUA2024 PREVIEW

A Preview of the Artificial Intelligence Plenary Discussion at AUA2024

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Introduction

As the frontier of health care rapidly evolves, we are thrilled to present an exclusive preview of an upcoming panel discussion at the AUA2024 conference that promises to delve deep into the transformative potential of artificial intelligence (AI) in urology. From enhancing diagnostic precision in prostate cancer through radiomics to revolutionizing bladder cancer treatment with pathomics and improving surgical planning and execution, this panel discussion is set to illuminate the myriad ways in which AI is reshaping health care (Figure).

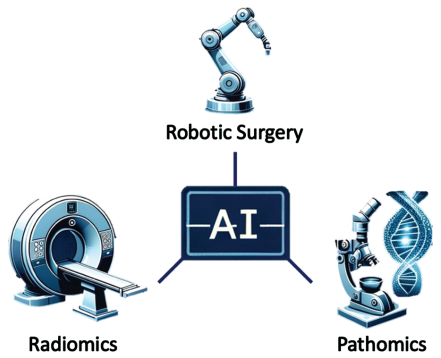

Figure. Overview of the plenary discussion. AI indicates artificial intelligence.

What Is AI/Machine Learning/Deep Learning Application in Surgery?

Dr Andrew J. Hung from Cedars-Sinai Medical Center will give an overview regarding "surgical AI," an emerging field at the intersect of surgery and AI, and explain the most commonly encountered terms.[1] AI stands as the general term under which machine learning (ML) and deep learning (DL) find their places.[2] AI's application in surgery manifests through algorithms and computational models designed to simulate human intelligence, offering advancements in diagnostic accuracy, patient-specific treatment plans, and operative precision. ML serves as a crucial subfield within AI, providing the means for computers to gain insights and make sense of data. AI aims to replicate human cognitive functions, and ML offers the methodologies necessary for this imitation. Through the analysis of data, ML algorithms enable AI systems to evolve and enhance their capabilities over time. DL, a specialized branch of ML, leverages intricate neural networks to handle sophisticated tasks. DL is characterized by its use of artificial neural networks modeled after the human brain's architecture. These networks comprise multiple layers of nodes or neurons, which process incoming data and relay them through the network. This structure allows for the learning of data's hierarchical features. DL is particularly adept at analyzing and identifying patterns within vast datasets, including images, sounds, and texts, by learning from unstructured data. The synergy of AI, ML, and DL in surgery not only propels the field towards unprecedented technological heights but also promises significant improvements in patient outcomes and health care efficiencies.

AI and Radiomics in Prostate Cancer

Dr Geoffrey A. Sonn from Stanford University will illuminate the profound impact of AI and radiomics on prostate cancer diagnostics and management. Investigations into AI's role in diagnosing prostate cancer are progressing quickly, offering the potential to improve every facet of the existing diagnostic approach, advancing the precision in detecting, characterizing, and stratifying prostate cancer risk, underscoring the crucial role of technology in tailoring patient-specific therapeutic strategies. While a vast amount of scholarly work discusses AI applications in prostate cancer detection, the majority of these innovations have not advanced to a stage where they can be implemented in clinical settings.[3] Dr Sonn will address the challenges of integrating these technological advancements into current clinical frameworks, emphasizing the necessity for ongoing research and multidisciplinary collaboration to bridge the gap between theoretical innovation and practical clinical application.

AI and Pathomics in Bladder Cancer

Dr Joseph C. Liao from Stanford University will use bladder cancer (BC) as an example to showcase how AI is used in pathomics. The examination of tumor tissue through pathology remains the gold standard in diagnosing and determining the risk level of bladder cancer. AI-enhanced pathology tools are emerging as significant aids in improving diagnostic precision and assisting in the risk assessment for BC patients, playing a crucial role in shaping treatment strategies and future outlooks. Several research teams have crafted DL algorithms capable of forecasting BC progression by analyzing clinical and pathological data.[4] These AI-driven models are pivotal for pinpointing patients at elevated risk, necessitating more intensive treatments or adjusted monitoring plans. This synergy of AI with traditional cytology and pathology is opening new paths for advancing BC treatment and enhancing patient care outcomes.

AI in Surgical Planning and Execution

Dr Prokar Dasgupata from King's College London will shed light on how AI can be used in surgical planning and execution. Computer vision, a science of using AI to analyze images and videos, is revolutionizing how surgeons perform and teach surgery. AI has been used in surgical phase recognition, in other words, recognizing different surgical steps and substeps, which can provide valuable information for surgical education and facilitate real-time surgical workflow monitoring for operating room management.[5,6] More granularly, AI can follow the motion of surgical instruments and recognize which exact surgical gesture is being used.[1,7] Those are the building blocks for more complex tasks such as intraoperative intelligent assistance or automatic surgery.

As we approach the AUA2024 conference, the anticipation for the "Artificial Intelligence Plenary Discussion" underscores the medical community's commitment to embracing the future. The insights from Drs Hung, Sonn, Liao, and Dasgupta exemplify the pioneering spirit of the urological field, showcasing AI's capacity to revolutionize not just urology but health care at large. As we delve into the complexities and potentials of AI, ML, and DL, let us move forward with the knowledge that the future of urology, powered by AI, is not just approaching–it's here. ■

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The Current State and Future Applications of Prostate-Specific Membrane Antigen in Urology

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There is a growing use and acceptance of prostate-specific membrane antigen (PSMA) targeted diagnostics and theranostics in prostate cancer. Undoubtedly, we have entered the PSMA era in prostate cancer.

PSMA Diagnostics for Staging

Three PSMA diagnostic agents have received FDA (Food and Drug Administration) approval over the past 5 years for staging and biochemical recurrence (BCR): Ga 68 PSMA-11 in 2020,[1] ^{18}F-DCFPyL in 2021,[2] and rhPSMA-7.3 in 2023.[3] PSMA imaging is now regarded as a standard of care staging imaging modality for high-risk prostate cancer in both the NCCN (National Comprehensive Cancer Network) and AUA/American Society for Radiation Oncology 2022 guidelines. While it was hoped that PSMA staging positron emission tomography (PET)/CT would significantly improve nodal staging in prostate cancer, it is limited in its detection of small nodal disease. While trials have found impressive specificities ranging from 92% to 98%, PSMA PET/CT has failed to demonstrate significant improvement in nodal staging sensitivity. Prospective trials have found a sensitivity of 25% to 40% for nodal detection when compared to histopathologic confirmation.[1-3]

Despite enthusiasm for PSMA imaging, questions remain as to how PSMA staging PET/CT should be effectively implemented into clinical practice. The existing evidence does not support omitting pelvic lymph node dissection in the setting of a negative PSMA PET/CT. Petersen et al evaluated Ga 68 PSMA-11 nodal staging accuracy compared to nodal histopathology and found the median size of true positive metastases to be 9 to 11 mm.[4] Conversely, the median false-negative nodal diameter was 4 mm with nearly one-third of the positive lymph nodes on histopathology being < 2 mm, highlighting the size limitation to PSMA imaging.[4] While highly specific, a negative PSMA scan is not sensitive enough to detect small nodal metastasis.

Furthermore, the clinical implications of a positive PSMA PET/CT in the setting of negative conventional imaging remain unclear. If nodal or bone metastatic disease are identified only on PSMA PET/CT, does this represent a unique biologic state in which local therapy remains a curative option? Conversely, would these findings exclude the patient from receiving potentially curative local therapy without level 1 evidence to support this change in management?

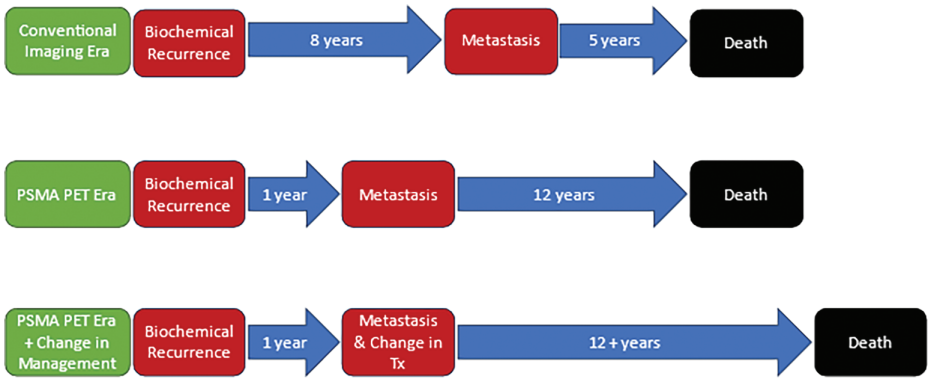

Figure 1. The natural history of biochemical recurrence.[9] PET indicates positron emission tomography; PSMA, prostate-specific membrane antigen; Tx, therapy.

PSMA Diagnostics for BCR

In the setting of BCR, PSMA PET/CT is also recommended as the preferred imaging option. The positive predictive value of Ga 68 PSMA-11 in assessing biochemically recurrent prostate cancer is reported to be 84% to 92%.[5] Likewise, for ^{18}F-DCFPyL positive predictive values have been demonstrated at 89% and 92% for rhPSMA-7.3.[6,7] While advancements have been made in our interpretation of PSMA imaging, there is much to be explored in the treatment algorithm of the PSMA-positive conventional imaging–negative BCR patient. Pound et al have previously shown that the median time from BCR (without treatment) to identifiable metastasis on conventional imaging was 8 years.[8] The median time to death was reported as an additional 5 years after the development of metastatic disease.[8] The potential to identify metastatic disease at an earlier state necessitates the need to investigate novel treatment strategies to prolong survival (Figure 1). PSMA PET/CT will improve staging via stage migration; however, PSMA PET/CT will only facilitate improved survival if we effectively act on this early diagnosis of radiographic metastasis. As PSMA PET/CT expands, we expect the role of metastasis-directed therapies to expand in parallel.

PSMA Diagnostics for Tumor Localization Within the Prostate

Although there is potential for PSMA to improve tumor localization within the prostate, significant study is still needed. The phase 2 PRIMARY trial demonstrated that, in biopsy-naïve patients, the addition of PSMA PET/CT to multiparametric MRI (mpMRI) improves the sensitivity of significant prostate cancer detection (97% vs 83%).[9] However, PSMA PET may not improve the specificity of cancer detection over mpMRI, leaving the challenge of false-positive findings.[9] To standardize the reporting of intraprostatic PSMA PET/CT findings, the PRIMARY score has been developed, which mirrors the mpMRI Prostate Imaging Reporting and Data System but requires validation.

PSMA Theranostics in Localized Prostate Cancer

PSMA theranostics leverages the specificity of PSMA binding to prostate cancer and selectively delivers radiation at a cellular level. The VISION trial (NCT03511664) led to FDA approval of ^{177}Lu-PSMA-617 in the treatment of late-stage metastatic castration-resistant prostate cancer.[10] This randomized phase 3 trial found that PSMA-bound β-emitting radionucleotides significantly improved overall survival.[10] The NCCN and AUA/Society of Urologic Oncology 2023 guidelines reflected this change in care with recommendations to offer ^{177}Lu-PSMA-617 to metastatic castration-resistant prostate cancer patients with a positive PSMA PET scan and progressive disease despite standard of care therapy. Multiple trials now seek to bring this novel treatment class to earlier disease settings. The LuTectomy trial (NCT04430192, Peter MacCallum Cancer Center) was a phase 1 single-arm study that recently demonstrated the potential feasibility and safety of ^{177}Lu-PSMA-617 prior to radical prostatectomy in patients with high-risk localized prostate cancer.[11] Furthermore, in 2024, Chapin et al will open the Nautilus trial (NCT06066437, MD Anderson Cancer Center) as the first randomized, controlled, neoadjuvant PSMA theranostic trial. This trial seeks to evaluate the role of neoadjuvant ^{177}Lu-PSMA-617 with and without androgen deprivation therapy in high-risk prostate cancer (Figure 2). Future trials will continue to assess the potential role of theranostics in both the neoadjuvant and adjuvant spaces and may one day join the urologist armamentarium.

Conclusions

Great strides have been made in our understanding and utilization of PSMA diagnostics and theranostics. While PSMA is rapidly

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THE CURRENT STATE AND FUTURE APPLICATIONS OF PROSTATE-SPECIFIC MEMBRANE ANTIGEN IN UROLOGY

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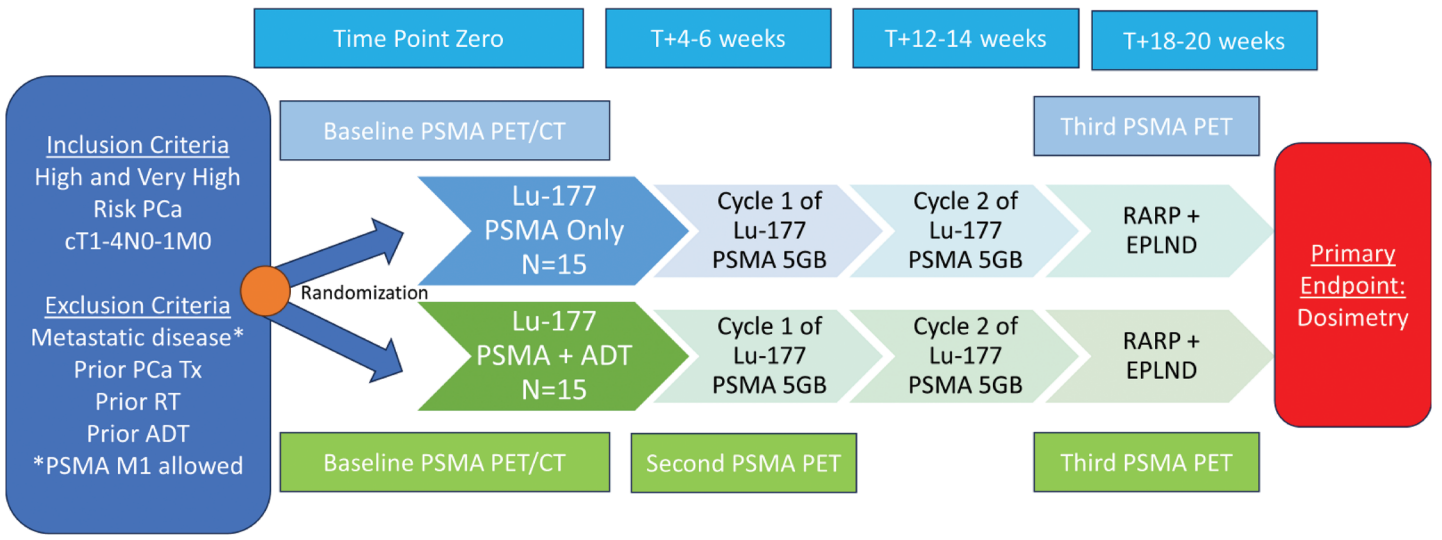

Figure 2. Nautilus trial design. ADT indicates androgen deprivation therapy; CaP, prostate cancer; ECOG, Eastern Cooperative Oncology Group; EPLND, extended lymph node dissection; Lu, lutetium; M1, stage M1; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; RARP, robot-assisted radical prostatectomy; t+, time; Tx, therapy.

changing practice, prospective trials are needed to understand the implications of management changes based on PSMA PET findings. Additionally, PSMA theranostics are being evaluated in early disease settings and may one day be included in the management algorithm for localized or recurrent prostate cancer. While we have firmly entered the PSMA era, it is imperative that we prioritize prospective clinical trials to effectively implement PSMA into practice. ■

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American Urological Association

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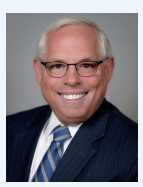

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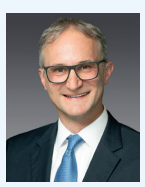

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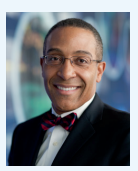
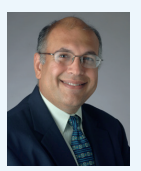


Byron D. Joyner, MD, MPA



Ajay K. Nangia, MBBS

Ubiquity of Biofilms on Penile Prostheses: Paradigm Shifts in Understanding of Device-Related Infection

Bradley J. Roth, BS
Cleveland Clinic Foundation, Ohio

Glenn T. Werneburg, MD, PhD
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Aaron W. Miller, PhD
Cleveland Clinic Foundation, Ohio

Petar Bajic, MD
Cleveland Clinic Foundation, Ohio

The penile prosthesis microbiome has been an area of increasingly active research. It was previously believed that biofilms, which are communities of microbial organisms that adhere to each other and a surface, were inherently associated with prosthesis infection.[1,2] However, studies recently published by our group have questioned these conclusions.

The earliest of these studies was centered around the hypothesis that penile biofilm composition would differ based on clinical indication for explantation.[3] In this study, 27 patients had penile prosthesis explanted for a variety of reasons including infection, pain, and mechanical failure. We swabbed the first encountered area of the device components and utilized subcutaneous tissue swabs as controls. We found that β-diversity, the similarity between microbial communities based on the presence/absence of specific microbes and their relative abundances, was not significantly different ($P = .16$) no matter the indication for explantation. Astonishingly, increased species richness (the degree of diversity) was associated with increased indwelling time and lower likelihood of infection. Put plainly, devices that remained implanted longer were less likely to become infected but showed a more diverse community of microbes on their surface. Metabolomic analyses, using mass spectrometry, demonstrated that *Staphylococcus* and *Escherichia/Shigella* were similarly enriched in the presence and absence of infection. While these organisms are commonly identified in culture-based studies of inflatable penile prosthesis infection,[4] our results demonstrate that it is not the simple presence of these uropathogens and their associated biofilms that lead to infection. Thus, the ubiquity of microbes, along with their respective biofilms and metabolites found in this study, refutes the dogma that biofilms always lead to infection and that biofilm prevention will prevent infectious sequelae.

We followed this study with a more robust approach to sampling and evaluating biofilms.[5] In this study we sampled all device components (cylinders, pump, and reservoir) and utilized sonication of whole device components to remove biofilms. We identified

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UBIQUITY OF BIOFILMS ON PENILE PROSTHESES

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biofilms via scanning electron microscopy throughout our samples regardless of infection status, validating the results of our prior study. Interestingly, 16S ribosomal RNA sequencing, which evaluates bacterial RNA only, demonstrated significantly different biofilm composition based on infection status ($P = .001$). When this analysis was repeated using more inclusive shotgun metagenomics (nonspecific sequencing of all microbial genes[6]), biofilm composition was similar regardless of indication for removal. Key results from this study found that biofilm composition, again measured by β-diversity, differed based on device manufacturer and between individual patients. This significance held across both 16S ribosomal RNA sequencing and shotgun metagenomics. Overall, the findings of this study add credence to the results of our earlier work and affirm that biofilms are found on all prosthesis device components. Furthermore, there appear to be underlying patient and device component factors driving differences in biofilm composition.

Altogether, our studies provide solid evidence for the presence of biofilms on both infected and noninfected penile prostheses. What remains unknown is the significance of biofilms on noninfected devices, and more importantly, what disruptions occur in the postimplant microbiome that lead to specific clinical sequelae like infection or pain. Future studies aimed at testing these disruptions may help elucidate why certain devices become infected while others do not. Doing so may inform future work aimed at making safer device coatings and preventing or treating clinical infections. We hope our work provides the foundation for future research to examine biofilms differently, and not solely as an indicator of infection. ■

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AUA2024 PREVIEW

Modern Innovation: Promise or Peril? AUA2024 Ramon Guiteras Lecture

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University of Illinois Chicago College of Medicine
University of Illinois Chicago College of Engineering

It's a great honor to be invited to deliver the Ramon Guiteras Lecture at AUA2024. When I was asked, the theme requested was "what in current technological advances should urologists be concerned about, such as generative AI (artificial intelligence) like ChatGPT?" (If you've been living under a rock for the last couple of years and haven't yet seen the thousands of articles and news features about the arrival of this relatively new form of AI, I encourage you to go to chat.openai.com, try it out for yourself, and see what you think.) Urologists are technophiles, and our approach to new technology is generally sanguine at worst and ardent at best as we incorporate new innovations into our care of patients. We've done that with endoscopes, neural stimulators, lasers, microscopes, robots, and much, much more, so my general feeling about ChatGPT and urology is that we'll find a way to make it benefit urological health. But let's take a closer look at what ChatGPT is, and even more importantly, what's new in our innovation toolbox and its education, because there's a lot going on there.

It's useful to look back to the birth of modern computation to understand what a large language model like ChatGPT can offer, because what was true almost 200 years ago is highly relevant today. Charles Babbage, a 19th century English mathematician, set out to build a mechanical device to generate tables of polynomials, the "difference engine." He was unable to complete it due to the primitive craftsmanship of the time. Amazingly, he then set out to design an even more flexible and robust computer that could attack any solvable mathematical problem, the "analytical engine." It could never be made in his era, but with the advent of the transistor in the second half of the 20th century, analytical engines can now be found everywhere, in our telephones, on our desks, in our cars, and nearly anywhere that benefits from programmable devices. Lord Byron's daughter, Ada Lovelace, a brilliant mathematician, studied Babbage's plans for the analytical engine and wrote much about it, in fact writing the very first computer program. But she also opined about its utility and wrote: "It is desirable to guard against the possibility of exaggerated ideas that might arise as to the powers of the Analytical Engine…. The Analytical Engine has no pretensions whatever to originate anything. It can do whatever we know how to order it to perform. It can follow analysis; but it has no power of anticipating any analytical relations or truths. Its province is to assist us in making available what we are already acquainted with."[1]

What Lady Ada wrote about the analytical engine is entirely true of ChatGPT. ChatGPT uses large swaths of digitally available material and rearranges them according to the likelihood that words, phrases, and sentences would follow. Although it can sound like us, it doesn't think like us, and it can't create in the unique way that biological humans do. So while it can function like a clever human imposter at times, it doesn't present the full panoply of human intelligence, and we should be able to easily tame this beast of our own construction for our own devices (Figure 1).

Figure 1. Don't be afraid of ChatGPT: it only makes "available what we are already acquainted with." Used with permission from Claire Niederberger.

Yet what is really promising in modern innovation are the tools that are suddenly ubiquitous, inexpensive, accessible, and easily understood. And we can use them in teaching innovation to our medical students, urological residents, and fellows, providing a powerful future workforce that not only cares for patients, but also creates the devices involved in that care (Figure 2).

One set of tools are small, inexpensive, easily programmed, yet highly powerful computers. The Arduino was invented in 2005 by 2 faculty at the Interaction Design Institute in Ivrea, Italy. It is typically programmed using Processing, an accessible language invented

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MODERN INNOVATION: PROMISE OR PERIL? AUA2024 RAMON GUITERAS LECTURE

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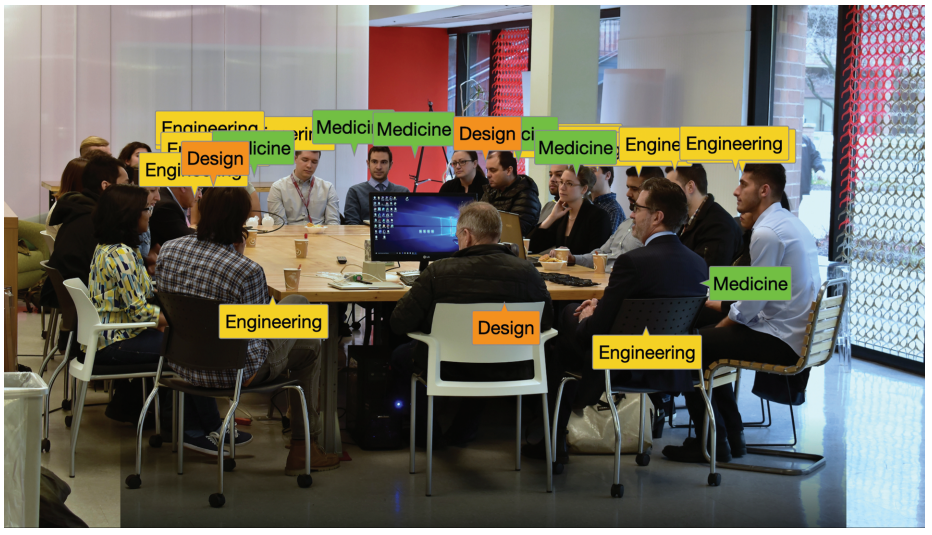

Figure 2. Teaching multidisciplinary innovation to urological learners.

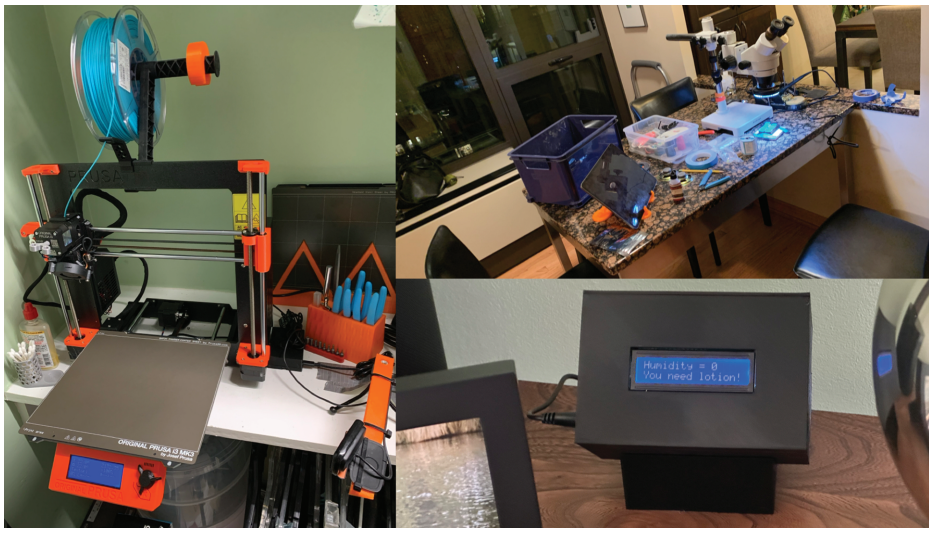

Figure 3. Modern innovation tools are so accessible they can fit in your closet and on your kitchen table.

in the MIT Media Lab designed to teach computer programming to non-STEM (science, technology, engineering, and mathematics) students. There is now a family of Arduinos, running upward from $20. The Raspberry Pi was invented in 2006 at the University of Cambridge, and it's a full computer with USB ports, HDMI for a high resolution monitor, Wi-Fi, and removable disk storage in the form of a micro SD (Secure Digital) card. It sports a full Linux operating system and runs upward from $5. Arduinos and Raspberry Pis have hardware inputs and outputs that can be attached to sensors, motors, displays, and pretty much anything that can be controlled electrically.

> "Another set of tools are 3D printers, and these are now available to consumers, costing as little as $200."

Another set of tools are 3D printers, and these are now available to consumers, costing as little as $200. With freely available design software, users can design and print just about any object. Combining the smarts of Arduinos and Raspberry Pis, anyone can create all sorts of machines and devices. (An example is the "Lotion-o-Meter" shown in Figure 3, which I made with a 3D printer in my closet and an Arduino that tells me when I need to apply lotion.)

We use these powerful tools to teach innovation to our urological learners. In a structured curriculum, students go through the process of problem identification, describing it and creating a high-level specification for what is necessary in a solution; intellectual property, market, and existing product research; ideating solutions; prototyping and testing them; and, finally, securing intellectual property for the unique solution. In the modern era, a team of contributors from varying disciplines, medicine, design, engineering, business, and law, work together in education to prepare the learner for a future of solving problems and making these solutions available to all. (An example of our educational group is shown in Figure 2.) It's an exciting time, and I'd say that the promise of modern innovation in medicine and urology far outpaces the peril. ■

1. Lovelace A. Notes upon the memoir, *Sketch of the Analytical Engine Invented by Charles Babbage, Esq.* Note G. Taylor and Francis; 1842.

AUA2024 PREVIEW

What We Have Learned About the Intersection of Urological Anomalies and Urinary Tract Infection

Nader Shaikh, MD
University of Pittsburgh Medical Center, Children's Hospital of Pittsburgh, Pennsylvania

In this short presentation we will review new development in the diagnosis, treatment, and imaging of children with UTI. The focus will be on selected high-impact manuscripts published in the last 2 to 3 years. Next, we will compare new data on the merits of various proposed strategies to individualize care of children with UTI. Can we easily and reliably identify children with high-grade vesicoureteral reflux, or children who are likely to experience febrile recurrences (Figure)? Or can we predict those who may end up with scarred kidneys? We will end with a comparison of proposed strategies and discuss possible future directions. ■

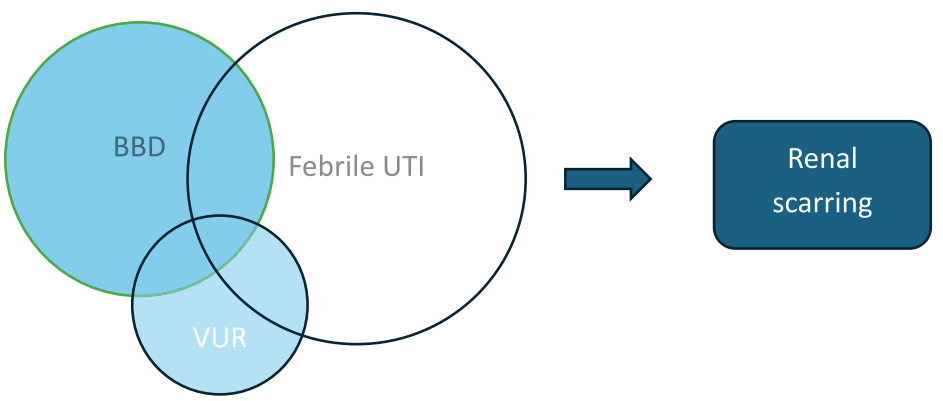

Figure. Risk factors for renal scarring are difficult to measure noninvasively. BBD indicates bladder-bowel dysfunction; VUR, vesicoureteral reflux.

AUA2024 PREVIEW

The History of Urology in 2024

Ronald Rabinowitz, MD
Historian, American Urological Association

John Phillips, MD
Historian-Elect, American Urological Association

Arthur L. Burnett II, MD
Curator, 2024 AUA History Exhibit

We look forward to welcoming all AUA attendees at the 2024 AUA History Exhibit, "Onward and Upward, Celebrating Black Urologists in America" at Booth #330 in the Science and Technology Exhibit Hall in San Antonio, Texas, curated by Arthur (Bud) Burnett, MD, and a curatorial team.

The legacy of Black urologists in America is a vital, pivotal history. It is critical to know the past, to be aware and knowledgeable of the present, and to prepare, to assist, and to lead in the development of the future. We must acknowledge the past in order to improve the future. The history of urology reflects the history of medicine and, in many ways, the history of the US, where we still confront racism and its legacy of dehumanization, invisibility, and silencing of Black Americans. The AUA now has its own committee on diversity, equity, and inclusion. Likewise, the book that accompanies this exhibit is necessary to illustrate the importance of diversity, equity, and inclusion in the education of future urologists, our health care environment, and the quality of our clinical care.

The American poet Pat Parker (1944-1989) described the challenge of learning from the past while moving forward with civility and respect. Her 1978 work "Movement in Black" includes the poem, "For the White Person Who Wants to Know How to Be My Friend."[1] She begins, "The first thing you do is to forget that I'm Black. Second, you must never forget that I'm Black." Parker's art urges us to see one another as human beings of complexity, individuality, and importance. Our heritage matters. Our knowledge matters. Our ethics matter. Our legacy as a profession that aims to heal, to prevent harm, and to strengthen humanity matters.

The Black experience in medicine and urology has been and still is marked by major challenges, especially in terms of representation. There has been no statistically significant increase in the representation of Black physicians in the US since 1900.[2] Accounting for changes in the US population, Black Americans only made up little more than 2% of all American physicians after 1965. In the US there are approximately 4.21 urologists per 100,000 population. If a Black person wishes to be cared for by a urologist of the same racial background, it is a challenge, as there is only 1 Black urologist for every 140,000 Black Americans. According to the 2022 AUA Census, of the 13,976 practicing urologists in the US, only an estimated 293 (2.2%) are Black.[3]

The 2024 AUA Forum on the History of Urology features 14 posters and 21 podium presentations on aspects of medical history. This 4-hour program kicks off with a medical ethics debate: "Can A.I. define 'Truth'?," with debaters Mack Roach, MD, and Elodi Dielubanza, MD.

The 2023 AUA Earl Nation Retrospectroscope Award from last year's presentations will be formally awarded to Elizabeth Ellis, MD, University of Rochester Medical Center, for her presentation and paper on "A Knight's Thrust: Was the Use of a Codpiece for Protection or for Exertion of Masculinity? An Evaluation Through History and Its Reemergence in Modern Times."

Thomas Oskinski, MD, University of Rochester Medical Center, will receive the 2023 Honorable Mention for his presentation and paper on "Refurbishing a Rusty Cystoscope into the Retrospectroscope Award."

The Bicknell Lecture will be given by Arthur (Bud) Burnett, MD, on "The Legacy of Black Urologists in America."

The 2024 William P. Didusch Art & History Award goes to Jennifer Gordetsky, MD, medical director of Anatomic Pathology and Surgical Pathology and professor of Pathology and Urology at Vanderbilt University Medical Center. A member of the AUA History Committee, Dr Gordetsky is also a previous AUA Earl Nation Retrospectroscope Award winner for her 2008 History Forum paper and presentation on "Urology and the Scientific Method in Ancient Egypt." ■

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2. Ly DP. Historical trends in the representativeness and incomes of Black physicians, 1900-2018. *J Gen Intern Med*. 2022;37(5):1310-1312.
3. American Urological Association. *The State of the Urology Workforce and Practice in the United States*. American Urological Association; 2022.

AUA2024 PREVIEW

The Great Sling Debate: Which Type of Sling Is Best in the Index Stress Urinary Incontinence Patient?

Adam P. Klausner, MD
Virginia Commonwealth University School of Medicine, Richmond

Michael E. Albo, MD
University of California, San Diego

Eric S. Rovner, MD
Medical University of South Carolina, Charleston

Suzette E. Sutherland, MD, MS
University of Washington School of Medicine, Seattle

Introduction

In the surgical treatment of stress urinary incontinence (SUI), there are multiple sling types and techniques available. As a result, the choices for patients and their surgeons can be both challenging and confusing. Fortunately, at this year's AUA Annual Meeting, a panel of experts will help sort out which type of sling is best for the index patient defined as "an otherwise healthy female who is considering surgical therapy for the correction of pure stress and/or stress-predominant mixed urinary incontinence who has not undergone previous SUI surgery."[1] Dr Michael Albo will argue in favor of the retropubic midurethral sling (MUS). Dr Eric Rovner stands by the autologous pubovaginal fascial sling (aPVS), and Dr Suzette Sutherland defends the newer single-incision sling (SIS). Which type is best? Read on for a preview of the "great sling debate."

Michael Albo, MD: Retropubic MUS

Since its introduction in the 1990s, the standard retropubic MUS has become the dominant procedure for the treatment of stress incontinence, and for good reason. It is a highly effective, durable, minimally invasive, and safe procedure. The technique is well described and can be standardized across patients and surgeons, which contributes to predictable and reproducible outcomes.

Numerous clinical trials and meta-analyses have consistently demonstrated the efficacy, durability, and safety of the

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THE GREAT SLING DEBATE: WHICH TYPE OF SLING

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standard MUS, and no procedure has demonstrated superior cure or improvement rates.[2] These studies have also shown long-term durability, with sustained efficacy and low rates of recurrence over extended follow-up.[3] Furthermore, reoperation rates are lower than with both single-incision and pubovaginal slings. The most recent Cochrane review of traditional suburethral slings identified only 14 comparative studies and concluded that they are probably no better, and may be less effective, than the MUS in terms of number of women continent in the medium term (1-5 years).[4] In addition, the MUS is clearly less invasive and has fewer complications.

There have been persistent efforts to minimize the adverse events associated with the standard MUS. The transobturator technique was developed to avoid the retropubic space, while the SIS was developed using a smaller volume of mesh and avoiding the pain associated with passing the trocar near the adductor longus tendon. While these techniques have demonstrated noninferiority to the standard retropubic MUS in regard to efficacy, they have not definitively established that they are safer or preferred by patients.

Indeed, the most recent Cochrane review of the SIS concluded that it remained uncertain whether the SIS offered lower rates of postoperative retention, repeat continence surgery, or surgery for mesh revision. In addition, it remained unclear if the single incisions led to higher rates of mesh exposure, extrusion, or erosion compared with retropubic MUS. There are still uncertainties regarding adverse events and longer-term outcomes. Therefore, longer-term data are needed to clarify the safety and long-term effectiveness of SIS compared to other midurethral slings.[5]

We have learned that cure or improvement of stress incontinence is not the only outcome that matters to our patients. Preferences regarding the risk and type of adverse events, invasiveness, length of recovery, durability of the procedure, and whether or not mesh is used are significant variables that must be considered. However, for the majority of my patients, the standard retropubic MUS is the procedure of choice.

Eric Rovner, MD: aPVS

It is generally agreed that no single procedure or intervention is optimal for all female patients with SUI. However, the aPVS is the gold standard and clearly the best choice. It is the predicate sling procedure upon which all subsequent slings are compared. Dozens of sling types and techniques have been introduced as alternatives to the aPVS over the last 140 years in order to shorten operative time; minimize intraoperative and postoperative recovery, pain, and convalescence; and/or reduce the cost or morbidity of female SUI surgery. The vast majority of these have failed in the short or long term due to unforeseen morbidity, complications, or lack of durability,

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THE GREAT SLING DEBATE: WHICH TYPE OF SLING

→ Continued from page 21

and have been consigned to the dustbin of surgical history. And although some of the remaining contemporary sling interventions may improve on one or more aspects as compared to the aPVS, none have yet been demonstrated to be superior to the aPVS for the treatment of female SUI.

The "index patient" as defined by the AUA[1] is somewhat limiting as it applies to only "virgin" SUI patients. However, the aPVS has been, and continues to be, the "go-to" procedure for both virgin[6] and complex patients with prior failed surgeries, with or without intrinsic sphincter deficiency, with or without urethral hypermobility, and with or without prior urethral surgery (fistula, urethral diverticula, etc).[6] Unlike the aPVS, mesh slings of any type are not often considered the first choice for redo cases of complex recurrent female SUI. Thus, it is not unreasonable to argue that the recognized gold standard for SUI, the aPVS, which is clearly effective as a salvage procedure for prior failed mesh slings,[7,8] should be also used for virgin patients as well.

Many procedures have been abandoned for the surgical treatment of female SUI over the years, and it is possible that several of the contemporary mesh sling procedures may, over time, have the same fate. Nevertheless, the aPVS remains the only procedure to be recognized and approved by all 7 iterations of the International Consultation on Incontinence[9] *and* all editions and updates to the AUA guideline on the surgical management of female stress urinary incontinence.[1]

Suzette Sutherland, MD: SIS

The mesh MUS is well established as a safe and efficacious treatment option for women with SUI, especially the index case associated with urethral hypermobility. To date, it is the most studied and most performed anti-incontinence procedure globally. Prior to the development of the MUS in the mid- to late-1990s, the aPVS was considered the "gold standard" for the surgical treatment of SUI due to both urethral hypermobility and intrinsic sphincter deficiency.[10] However, with the addition of the MUS to the surgical armamentarium, that position has been challenged. Although a recent meta-analysis involving almost 16,000 patients noted similar efficacy between MUS and aPVS at 5 years, longer-term (>5 year) comparative data are still lacking. And when evaluating both efficacy and safety, the superiority of the MUS was confirmed.[11]

> "Dozens of sling types and techniques have been introduced as alternatives to the aPVS over the last 140 years in order to shorten operative time; minimize intraoperative and postoperative recovery, pain, and convalescence; and/or reduce the cost or morbidity of female SUI surgery. The vast majority of these have failed in the short or long term due to unforeseen morbidity, complications, or lack of durability, and have been consigned to the dustbin of surgical history."

The mechanism of action of the MUS is based on the "Integral Theory" by Petros and Ulmsten (1990), which describes dynamic kinking of the midurethra by the pubourethral ligament during valsalva. Accordingly, this type of sling was designed as a tension-free procedure for women with SUI due to urethral hypermobility.[12] With advancing innovation over the ensuing decades, the MUS procedure and mesh sling devices have evolved with the intent of providing improved surgical safety while maintaining the same excellent efficacy. This led to the introduction and Food and Drug Administration approval of the retropubic transvaginal tape (TVT; 1996), transobturator tape (TOT; 2003), and the SIS (2008).

Previous concerns about "immature dates" pertaining to the long-term efficacy of the SIS[13] are now no longer valid. Today, 15 years after the introduction of the SIS to the US market, sufficient data with level I evidence notes equal, non-inferior efficacy compared to TVT and TOT in the index patient with no deterioration over time (comparing 2 to 10 years–with objective and subjective cure rate percentiles repeatedly in the high 80s).[14] And, as reported in a very recent 2023 Cochrane review, SIS "may be as effective as retropubic slings" and "are as effective as transobturator slings."[5] Although the TVT is noted to have slightly enhanced cure durability, this comes at the cost of higher intraoperative complications and postoperative voiding dysfunction.[11] Although rare, devastating and even life-threatening complications within the retropubic space and transobturator/thigh space have occurred. This provided the inspiration for further MUS innovation; and thus, the SIS was born.

By eliminating the need to enter either the retropubic or transobturator/thigh spaces, the SIS provides a safer option for MUS delivery. Indeed, the advantages of the SIS are mainly related to improved safety features including minimal mesh burden; limited surgical dissection; shorter blind trocar passages; reduced potential for surrounding organ perforation, occult bleeding, or hematoma formation; and a more secure anchoring mechanism with earlier return to daily activities. When evaluating other mesh-related complications with the MUSs, the most common–mesh extrusion into the vagina–is exceedingly rare (3%-5%) in trained hands and readily managed, as noted by contemporary data, regardless of the mode of MUS delivery. Although postoperative urinary retention, obstructive voiding symptoms, and/or de novo voiding dysfunction with urgency are possible with any type of anti-incontinence procedure, the incidence associated with aPVS is highest (22%-30%), followed by the TVT, the TOT, and then the SIS. With these advances and the subsequent long-term efficacy data now available, the AUA/SUFU (Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction) guidelines 2023 update for the surgical treatment for female SUI now acknowledges the SIS as an equally viable option for the surgical treatment of SUI in the index patient.[1] ■

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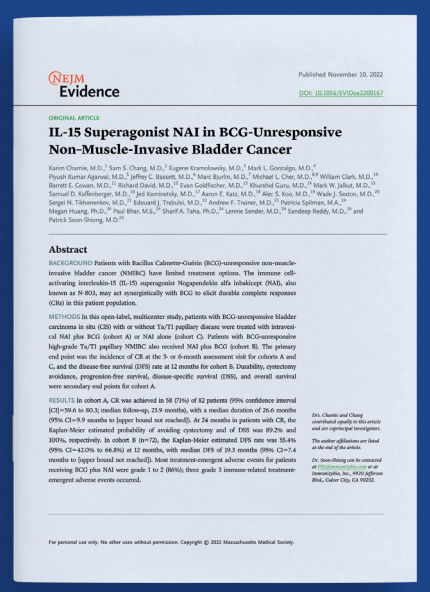

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ORIGINAL ARTICLE

IL-15 Superagonist NAI in BCG-Unresponsive Non-Muscle-Invasive Bladder Cancer

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Abstract

BACKGROUND Patients with Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle-invasive bladder cancer (NMIBC) have limited treatment options. The immune cell-activating interleukin-15 (IL-15) superagonist Nogapendekin alfa inbakicept (NAI), also known as N-803, may act synergistically with BCG to elicit durable complete responses (CRs) in this patient population.

METHODS In this open-label, multicenter study, patients with BCG-unresponsive bladder carcinoma in situ (CIS) with or without Ta/T1 papillary disease were treated with intravesical NAI plus BCG (cohort A) or NAI alone (cohort C). Patients with BCG-unresponsive high-grade Ta/T1 papillary NMIBC also received NAI plus BCG (cohort B). The primary end point was the incidence of CR at the 3- or 6-month assessment visit for cohorts A and C, and the disease-free survival (DFS) rate at 12 months for cohort B. Durability, cystectomy avoidance, progression-free survival, disease-specific survival (DSS), and overall survival were secondary end points for cohort A.

RESULTS In cohort A, CR was achieved in 58 (71%) of 82 patients (95% confidence interval [CI]=59.6 to 80.3; median follow-up, 23.9 months), with a median duration of 26.6 months (95% CI=9.9 months to [upper bound not reached]). At 24 months in patients with CR, the Kaplan-Meier estimated probability of avoiding cystectomy and of DSS was 89.2% and 100%, respectively. In cohort B (n=72), the Kaplan-Meier estimated DFS rate was 55.4% (95% CI=42.0% to 66.8%) at 12 months, with median DFS of 19.3 months (95% CI=7.4 months to [upper bound not reached]). Most treatment-emergent adverse events for patients receiving BCG plus NAI were grade 1 to 2 (86%); three grade 3 immune-related treatment-emergent adverse events occurred.

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SCAN ME

N-803 is investigational. Safety and efficacy have not been established by any Health Authority or Agency, including the FDA.