Strategies to mitigate impact of intravenous ICM shortage

SEXUAL DYSFUNCTION
Study highlights trends in shockwave therapy for erectile dysfunction

PROSTATE CANCER
Aggressive prostate cancer diagnoses are on the rise

BLADDER CANCER
Robotic cystectomy is effective, but overall clinical impact is uncertain

PRACTICE MANAGEMENT
What to know about billing for unlisted codes

See reverse side for a message from AACU
Dear AACU Members:

More than 50 years ago, the AACU became the first national organization solely dedicated to advocacy on behalf of clinical urologists’ interests. At the time, Medicare was a new program and the federal government’s role in healthcare quickly grew by leaps and bounds. Today, the AACU continues to steadfastly advance health policies that protect our patients, practices, and profession through initiatives such as UROPAC, the AACU State Advocacy Network, and our recent partnership with Urology Times.

This strategic alliance gives us the opportunity to share news of our work, and the work of AACU members, on a national stage, including showcasing members in Urology Times publications and on the website at www.urologytimes.com/sap-partner/aacu.

In addition to opportunities to publish, the partnership brings AACU members access to case-based roundtable sessions and discounted educational programs. We are pleased to be able to provide these valuable resources and hope that you and your colleagues find them informative. If you would like additional copies of this publication sent to your office, please email info@aacuweb.org.

We are excited about the partnership and look forward to highlighting AACU and its members through our collaboration with Urology Times.

Best regards,

Damara L. Kaplan, PhD, MD
President
American Association of Clinical Urologists
www.aacuweb.org

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Strategies to mitigate impact of intravenous ICM shortage

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Publisher’s Note

Reflecting on the AUA Annual Meeting

It is incredible to think we are already in the second half of 2022. It has been a busy year for the editorial team of *Urology Times®,* particularly with the return of in-person conferences. At this year’s American Urological Association (AUA) Annual Meeting in New Orleans, Louisiana, our team held its first in-person editorial advisory board meeting since 2019. The well-attended meeting was full of robust discussion, generating plenty of ideas for content to continue serving the needs of the practicing urologist. One suggestion that was raised was increased involvement of urologists who are just starting out in practice. If you are approximately 1 to 5 years removed from your residency/fellowship and are interested in collaborating with *Urology Times®* on future content initiatives, please contact the editors at UTeditors@mjhlifesciences.com.

Speaking of the AUA Annual Meeting, you’ll find plenty of conference coverage in this month’s issue, from article recaps of key content initiatives, please contact the editors at UTeditors@mjhlifesciences.com. Our columns this month include Diversity in Urology, in which *Urology Times®* Editorial Council Member Mary K. Samplaski, MD, contributes a piece on ethnic differences in men undergoing reproductive urology evaluation. She writes, “Racial differences exist for men undergoing fertility evaluation by a reproductive urologist…. As clinicians, we must better understand how race plays a role in fertility therapy.”

In Practice Matters, Robert A. Dowling, MD, analyzes Medicare Part D to help you understand your prescribing patterns of drugs for overactive bladder (OAB). “The 2019 Medicare data suggest urologists prescribe OAB drugs to Part D beneficiaries in higher quantities than most other specialists and tend to use more types of drugs and more expensive drugs [mirabegron] than nonurology specialties,” Dowling concludes.

In Money Matters, Jeff Witz, CFP, provides advice on surviving down markets. Finally, in Malpractice Consult, Acacia Brush Perko, Esq, reviews a case involving a wrong testicle being removed during an orchietomy, resulting in $870,000 being awarded to the plaintiff. Thanks for reading. •

**REFERENCE**


*UrologyTimes.com*
Novel testosterone undecanoate capsule launches in US
Testosterone undecanoate (Tlando), an oral testosterone replacement therapy for the treatment of men with hypogonadism, has officially launched in the US market. The FDA approved testosterone undecanoate capsules in March 2022 for the treatment of patients with either:
- Primary hypogonadism (congenital or acquired), defined as testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchectomy, Klinefelter syndrome, chemotherapy, or toxic damage from alcohol or heavy metals
- Hypogonadotropic hypogonadism (congenital or acquired), defined as gonadotropin or luteinizing hormone-releasing hormone deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation
The pivotal trial supporting approval of the oral testosterone undecanoate was Study 16-002 (NCT03242590), which included 95 hypogonadal participants. All patients received testosterone undecanoate at 225 mg twice daily for approximately 24 days. Patients’ treatment doses were not titrated. The median patient age was 56 years (range, 29-74), 70% were obese (body mass index ≥ 30 kg/m²), 50% had a history of hypertension, and 23% had a history of type 2 diabetes. Overall, 81% of patients were White, 16% were Black, 2% were of mixed race, and 1% were Asian.
The primary study end point was the percentage of patients who, on the final visit of the study, reached a 24-hour average serum testosterone concentration within the normal range (300-1080 ng/dL). This end point was reached with 80% (95% CI, 72%-88%) of patients achieving this benchmark.

REFERENCES

NCCN recommends IsoPSA test for up-front prostate cancer risk assessment
The IsoPSA test has been added to the National Comprehensive Cancer Network prostate cancer guidelines for early detection of the disease, according to Cleveland Diagnostics, the developer of the assay. The blood-based, noninvasive IsoPSA test is used before initial biopsy to assess the likelihood that a patient has high-grade prostate cancer.

Eric Klein, MD, fellow, Stanford University Distinguished Careers Institute and emeritus professor and chair, Glickman Urological and Kidney Institute, Cleveland Clinic, was the lead investigator on a real-world clinical validation study of IsoPSA published in the journal Urology Practice. The study included a diverse group of 38 community-based and academic sites within the Cleveland Clinic health system. There were 900 patients under evaluation for prostate cancer who were enrolled at these locations. Of these, 734 met study inclusion criteria, which comprised minimum age 50 years, total serum prostate-specific antigen level of at least 4 ng/mL and less than 100 ng/mL, and no history of prostate cancer. The study investigators assessed biopsy recommendations of participating clinicians before and after receipt of IsoPSA results.
The results showed that in men with total PSA equal to or greater than 4 ng/mL, IsoPSA led to a 55% (284 vs 638) net reduction in prostate biopsy recommendations. There was also a 9% reduction in MRI recommendations.

“What we found was really remarkable and it was what we had hoped for,” said Klein. “We’d rather not find on labs,” said Klein.

REFERENCE

UroPipeline
UPDATES ON DRUGS, DEVICES, AND TESTS by Jason M. Broderick

NCCN, SNMMI add piflufolastat F 18 to guidelines for prostate cancer imaging
The National Comprehensive Cancer Network and the Society of Nuclear Medicine and Molecular Imaging guidelines now include the use of piflufolastat F 18 (Pylarify), along with all approved prostate-specific membrane antigen (PSMA)–PET imaging agents, for the selection of patients with prostate cancer to receive PSMA-targeted radionuclide therapy.
The FDA approved the PSMA-PET imaging agent piflufolastat F 18 in 2021 for identifying suspected metastasis or recurrence of prostate cancer. The approval was supported in large part by findings from the phase 3 CONDOR trial (NCT03739684), in which 63.9% of men with biochemically recurrent prostate cancer who had no evidence of disease on standard-of-care imaging had a change in intended management after their 18F-DCFPyL–PET/CT scan.
The primary end point was correct localization rate (CLR), defined as percentage of patients with a 1:1 correspondence between at least 1 lesion identified by PyL–PET/CT and the composite standard of truth (pathology, correlative imaging, or PSA response). PyL scans were read by 3 blinded independent central readers.

Detection of disease as manifested by a positive 18F-DCFPyL–PET/CT scan was 65.9%, 59.6%, and 59.1% by the 3 readers. The pre-specified criterion for CLR success was for the lower limit of the 95% CI to exceed 20% for at least 2 of the 3 readers. For every reader, the lower bound of the 95% CI for the CLR was well above the 20% benchmark, meeting the primary end point of the study.

REFERENCES
Treatment intensification for high-risk localized disease: The time has come

Improved outcomes in men with advanced prostate cancer have been anchored to advances in hormonal therapy over the past 80 years. It is acknowledged that the pioneering work of Charles Huggins, MD, and Clarence V. Hodges, MD, in 1941 set the path for our understanding of androgen responsiveness of prostate cancer and the role of androgen deprivation therapy (ADT) in treatment of those with advanced and metastatic disease.1

Approximately 50 years ago, the development of long-acting luteinizing hormone-releasing hormone (LHRH) agonists revolutionized the hormonal treatment of prostate cancer, allowing men treatment that could avoid the stigma associated with surgical castration and allow for intermittent therapy in certain clinical scenarios.2 The development of first-generation nonsteroidal antiandrogens was another advancement that not only provided a mechanism to suppress the flare associated with LHRH agonists but also allowed for trials of combined androgen blockade with the addition of an antiandrogen as compared with LHRH or orchietomy alone. However, the modest survival benefit of adding these antiandrogens to conventional testosterone suppression tempered widespread enthusiasm.1,2

Although use of docetaxel chemotherapy was associated with benefit among men with castration-resistant prostate cancer, the real excitement for its use became evident when it was studied earlier in the disease state. The combination of chemotherapy and ADT in men with newly diagnosed metastatic disease was truly dramatic in its impact. The addition of docetaxel combined with LHRH therapy was a game changer, as it dramatically improved outcomes for men with newly diagnosed metastatic prostate cancer. Two trials—CHAARTED (NCT00309985) and STAMPEDE (NCT00268476)—both demonstrated improved overall survival with the addition of chemotherapy as compared with traditional ADT.3,4 Shortly thereafter, the addition of androgen-targeted therapies combined with traditional LHRH demonstrated improved overall survival as compared with LHRH therapy alone. Both the LATITUDE (NCT01715285) and STAMPEDE trials demonstrated survival benefit with the addition of an androgen synthesis inhibitor (abiraterone [Zytiga] and prednisone) to traditional LHRH therapy.5,6 Also, the addition of second-generation androgen receptor blockers (enzalutamide [Xtandi] and apalutamide [Erleada]) plus LHRH resulted in significant improved survival compared with the LHRH therapy.7,8 Currently, in the United States, there has been a tendency toward treatment with chemotherapy for those patients with high-volume metastatic burden, as well as androgen receptor–targeted therapy for those who have lower-volume metastatic disease and who are less fit for chemotherapy.

That brings us to the current state, where new data have revealed that patients with metastatic prostate cancer benefit from treatment intensification or triple therapy. In the PEACE-1 trial (NCT01957436), it was shown that the combination of docetaxel, LHRH, and abiraterone was superior to docetaxel plus LHRH therapy alone.9 In addition, the ARASENS trial (NCT02799602) demonstrated the combination of docetaxel, LHRH, and darolutamide (Nubeqa) was superior to docetaxel plus LHRH therapy, with significantly improved overall survival.10 Still to be decided is how to select patients for this treatment intensification coupled with the timing of the sequencing, of course weighing the potential increase in adverse effects.

These advances in androgen receptor–targeted therapy now coupled with chemotherapy are important and have significantly improved outcomes for men with metastatic disease. Over the years, we have improved the quality of life of men with advanced prostate cancer and have been able to extend the length of their lives by years. However, as exciting as these improvements have been, we are still facing the reality that we are not yet curing advanced or metastatic prostate cancer. We have seen the most impressive outcomes when 2 principles are adhered to: (1) treatment earlier in the disease state and (2) intensifying the treatment regimen.

However, earlier is a relative term and, in my opinion, not early enough. What we still need to trial is the use of treatment intensification or triple therapy in men with high-risk localized and/or locally advanced disease. The use of novel prostate-specific membrane antigen PET scans will allow for more accurate staging, and the opportunity for biomarker incorporation will allow for future patient selection. These studies could come in the form of neoadjuvant or adjuvant therapy prior to either surgery or radiation. The table is now set for a run at the elusive cure for men with truly high-risk disease. I certainly hope we don’t have to wait another half century to see this promise delivered to our patients.
Study highlights trends in shockwave therapy for erectile dysfunction

Treatment is performed primarily by nonurologists, researchers report

JASON M. BRODERICK
Associate Editorial Director, Urology Times®

A
mid the growing direct-to-consumer market for shockwave therapy (SWT) as a treatment for erectile dysfunction (ED), a study published in *Urology Practice* assessed emerging trends for the treatment across 8 large US cities.1 The investigators identified 152 clinics across the cities that offered SWT as an ED treatment. Approximately two-thirds (65%) of the clinics had comprehensive information available on their SWT usage. Urologists made up only 25% of SWT providers at the clinics, and 13% of the providers were not physicians.

Based on individual patient circumstance, therapy ranged from 1 treatment course to indefinite treatment courses, at an average price of $1338.28 for a full treatment course. The average cost of 1 individual session of a given SWT treatment course was $491.22.

“SWT, as a restorative therapy for ED, is performed primarily by nonurologists and is not standardized. Direct-to-consumer marketing is used to target distressed men. This study highlights concerning trends in major metropolitan markets, given the substantial financial impact for patients and inconsistent credentials among providers. Further, these findings suggest that patients are frequently seeking care for ED from nonurologists,” wrote the study authors, led by James M. Weinberger, MD, MBA.

The 8 US cities used for the study were Los Angeles, New York, Houston, Philadelphia, Atlanta, Boston, Dallas, and Washington, DC. Google was used to identify SWT providers in these metropolitan areas. The search terms used were “shockwave therapy for erectile dysfunction in [city],” “shockwave therapy for ED in [city],” and “GAINSWave in [city].” To gather the data, the investigators implemented a “secret shopper” approach, whereby they called the clinics to collect provider, price, and treatment course information.

The investigators found there was a lack of standardization across the clinics regarding the use of focused SWT vs acoustic or radial wave therapy, location of shock wave administration (eg, perineal, penile), and treatment protocol. Treatment courses consisted of a wide variety of session totals, with 6 being the most common. There was no consistency regarding the devices used for the procedure, the number of shocks during each session, or the energy and frequency settings.

“The investigators identified 152 clinics across the cities that offered SWT as an ED treatment. Approximately two-thirds (65%) of the clinics had comprehensive information available on their SWT usage. Urologists made up only 25% of SWT providers at the clinics, and 13% of the providers were not physicians.”

There were 18 different provider types among the physicians offering SWT. The investigators specifically drew attention to the fact that the fourth most common provider type among physicians were those trained in obstetrics and gynecology. “These physicians see no male patients throughout the entirety of their training, including no formal instruction in the pathogenesis and treatment of male sexual dysfunction,” the authors wrote.

In almost half (n = 3) of the cities, SWT was offered by as many as or more nonphysician providers than urologists. Nonphysician SWT providers included physician assistants, nurse practitioners, chiropractors, and naturopathic providers. There was high variation in the cost of SWT treatment courses, from a low of $600 for the set of sessions at one Atlanta clinic to a high of $16,200 at a New York location.

In an accompanying editorial2 published simultaneously with the article, Jonathan Rubenstein, MD, of Chesapeake Urology, stressed the importance of urologists fully taking charge across the board in the evaluation and treatment of patients with ED. “We all agree that urologists are best qualified to appropriately evaluate and treat patients with ED [because of] our advanced training and expertise in genitourinary physiology and pathophysiology,” Rubenstein wrote.

“We must own this space,” Rubenstein wrote. “We must understand which patients may benefit from which therapies and do everything we can to get patients into our offices for a proper evaluation and discussion of treatment options, even if it means offering alternative therapies. If we do, we must be honest with patient risks, including financial risks, and explain if a therapy is unlikely to work for them and not offer it to them if they are unlikely to benefit. We can’t control if others do so, and we can’t control if a patient ultimately seeks care elsewhere or does not follow our recommendations. However, at least we afforded them with the best possible medical advice and care based on our expertise.”

**REFERENCES**


Aggressive prostate cancer diagnoses are on the rise

Investigators also report lower rates of treatment of low-risk disease

JASON M. BRODERICK
Associate Editorial Director, Urology Times®

The downgrade of prostate-specific antigen (PSA) screening over the past 15 years has reduced the overdiagnosis and overtreatment of low-grade prostate cancer. But simultaneously, an increase has occurred in the rate of metastatic cancer at diagnosis, according to recent study findings.

“To our knowledge, this is the first study to demonstrate nationally that low-grade prostate cancer is no longer the most commonly diagnosed type of prostate cancer,” said senior author Jim C. Hu, MD, MPH, Ronald P. Lynch Professor of Urologic Oncology at Weill Cornell Medicine and director of the NewYork-Presbyterian LeFrak Center for Robotic Surgery in New York, New York, in a news release.1 “One of the weaknesses of PSA/prostate cancer screening was that it led to overdetection of indolent cancers that would not harm men, subjecting them to anxiety and future testing.”

In 2012, after concluding that the benefit of PSA screening did not outweigh the risks of overdiagnosis and overtreatment of low-grade prostate cancer, the US Preventive Services Task Force (USPSTF) issued a grade D recommendation against the use of PSA screening in the general US population, regardless of age. The current USPSTF PSA screening policy has been slightly changed, with a grade C recommendation for men aged 55 to 69 years; thus, in this population an individual decision on screening should be made based on discussion with one’s physician or clinician of the potential benefits and risks. For men aged 70 or older, the USPSTF recommends against any PSA-based screening (grade D recommendation). The panel also does not recommend screening for men younger than 55 years.

In their study,2 Hu et al sought to determine the overall impact of the screening downgrade on Gleason grade group (GG) at diagnosis and radical prostatectomy (RP) pathology. Using data from the Surveillance, Epidemiology, and End Results Program, the investigators identified 438,432 men with newly diagnosed prostate cancer in the period from 2010 to 2018. The study results were published in the Journal of the National Cancer Institute.

During this 8-year period, the rate of metastases at diagnosis increased from 3.0% to 5.2% (P < .001). The investigators linked this rise to the decrease in PSA screening, and suggested risk-stratified screening using MRI or biomarkers as a potential solution to maintaining the progress in reducing overdiagnosis or overtreatment while not missing these aggressive cancers.

The upside of what Hu et al found was that the incidence of low-grade prostate cancer (GG1) per 100,000 cases decreased from 52 to 26 cases (P < .001). As a proportion of all prostate cancer cases, the incidence of GG1 decreased from 47% to 32% (P < .001). At RP pathology, the incidence of GG1 decreased from 32% to 10% (P < .001).

“The fact that only 10% of radical prostatectomy specimens demonstrate low-grade prostate cancer indicates that even when low-grade cancer is diagnosed, it is being treated much less frequently,” Hu said. “This demonstrates that there has been acceptance of active surveillance, also known as monitoring with curative intent, among doctors and patients nationally.”

“It is encouraging to see that urologists in the United States have moved away from overutilization of radical therapies for the management of low-risk prostate cancer,” added first author Leonardo D. Borregales, MD, a urologic oncology fellow at Weill Cornell Medicine Department of Urology, in the news release.

REFERENCES
MEN LIVED 2X LONGER WITHOUT CANCER SPREADING\textsuperscript{1,2}  
40.4 months vs 18.4 months for ADT alone  
\textbf{HR: 0.41, 95\% CI: 0.34-0.50, P=0.0001 (intent-to-treat).}

REDUCED RISK OF DEATH BY NEARLY A THIRD\textsuperscript{1,3}  
31\% reduction in the risk of death vs ADT alone  
\textbf{Secondary endpoint: HR: 0.69, 95\% CI: 0.53-0.88, P=0.003. Medians not estimable.}

\section*{INDICATION}
NUBEQA\textsuperscript{\textregistered} (darolutamide) is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer.

\section*{IMPORTANT SAFETY INFORMATION}

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

\subsection*{Adverse Reactions}
Serious adverse reactions occurred in 25\% of patients receiving NUBEQA and in 20\% of patients receiving placebo. Serious adverse reactions in ≥1\% of patients who received NUBEQA were urinary retention, pneumonia, and hematuria. Overall, 3.9\% of patients receiving NUBEQA and 3.2\% of patients receiving placebo died from adverse reactions, which included death (0.4\%), cardiac failure (0.3\%), cardiac arrest (0.2\%), general physical health deterioration (0.2\%), and pulmonary embolism (0.2\%) for NUBEQA.

Adverse reactions occurring more frequently in the NUBEQA arm (≥2\% over placebo) were fatigue (16\% vs 11\%), pain in extremity (6\% vs 3\%) and rash (3\% vs 1\%).

Clinically significant adverse reactions occurring in ≥2\% of patients treated with NUBEQA included ischemic heart disease (4.0\% vs 3.4\% on placebo) and heart failure (2.1\% vs 0.9\% on placebo).

\subsection*{Drug Interactions}
\textbf{Effect of Other Drugs on NUBEQA} – Combined P-gp and strong or moderate CYP3A4 inducers decrease NUBEQA exposure, which may decrease NUBEQA activity. Avoid concomitant use.

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

\textbf{IMPORTANT SAFETY INFORMATION}
For your patient with non-metastatic castration-resistant prostate cancer (nmCRPC)

HELP HIM LIVE FOR WHAT HE LOVES

PROVIDED THE RELIEF OF AN EXTRA
15 MONTHS WITHOUT PAIN PROGRESSION\(^1,3\)∗

40.3 months vs 25.4 months for ADT alone
Secondary endpoint: HR: 0.65, 95% CI: 0.53-0.79, P<0.001.

POSTPONED CYTOTOXIC CHEMOTHERAPY—
MORE TIME WITHOUT CHEMO\(^1,3\)∗

42% risk reduction in time to chemo vs ADT alone
Secondary endpoint: HR: 0.56, 95% CI: 0.44-0.76, P<0.0001. Medians not estimable.

CHOOSE NUBEQA\(^{®}\) 1st FOR EXTENDED SURVIVAL\(^{1,3}\) NUBEQAHCP.COM

Drug Interactions (cont’d)
Effects of NUBEQA on Other Drugs – NUBEQA inhibits breast cancer resistance protein (BCRP) transporter. Concomitant use increases exposure (AUC) and maximal concentration of BCRP substrates, which may increase the risk of BCRP substrate-related toxicities. Avoid concomitant use where possible.
If used together, monitor more frequently for adverse reactions, and consider dose reduction of the BCRP substrate.
NUBEQA inhibits OATP1B1 and OATP1B3 transporters. Concomitant use may increase plasma concentrations of OATP1B1 or OATP1B3 substrates. Monitor more frequently for adverse reactions and consider dose reduction of these substrates.
Review the prescribing information of drugs that are BCRP, OATP1B1, and OATP1B3 substrates when used concomitantly with NUBEQA.

Metastasis-free survival (MFS) was the primary endpoint, and overall survival (OS) was a key secondary endpoint.\(^1\)

*Time to pain progression was defined as at least a 2-point worsening from baseline of pain score on BPI-SF (a validated health-related quality-of-life instrument) or initiation of opioids and reported in 28% of all patients on study.

Study design
The efficacy and safety of NUBEQA were assessed in a randomized, double-blind, placebo-controlled phase III study (ARAMIS) in nmCRPC patients on ADT with a PSA doubling time ≤10 months. 1509 patients were randomized 2:1 to 600 mg NUBEQA twice daily (n=955) or placebo (n=554). MFS was defined as time from randomization to time of first evidence of BICR-confirmed distant metastasis or death from any cause ≤33 weeks after the last evaluable scan, whichever occurred first. Treatment continued until radiographic disease progression, as assessed by CT, MRI, \(^{14}C\)bone scan by BICR, unacceptable toxicity, or withdrawal\(^1,3\).

ADT=androgen deprivation therapy; HR=hazard ratio; CI=confidence interval; BPI-SF=Brief Pain Inventory Short Form; PSA=prostate-specific antigen; BICR=blinded independent central review; CT=computed tomography; MRI=magnetic resonance imaging.

Please see the following page for the brief summary of Prescribing Information.
**NUBEQA** (darolutamide) tablets, for oral use

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

**CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION**

1. **INDICATIONS AND USAGE**
   NUBEQA is indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer (mCRPC).

2. **CONTRAINDICATIONS**
   None.

3. **WARNINGS AND PRECAUTIONS**
   3.1 Embryo-Fetal Toxicity
   The safety and efficacy of NUBEQA have not been established in females. Based on its mechanism of action, NUBEQA can cause fetal harm and loss of pregnancy when administered to a pregnant woman (see Clinical Pharmacology (12.3)).

   Advise males with female partners of reproductive potential to use effective contraception during treatment and for at least 1 week after the last dose of NUBEQA (see Use in Specific Populations (8.7, 8.8)).

4. **ADVERSE REACTIONS**
   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.

   ARAMIS, a randomized, double-blind, placebo-controlled, multicenter clinical trial, enrolled patients who had non-metastatic castration-resistant prostate cancer (mCRPC). In this study, patients received either NUBEQA or placebo daily for 800 mg, a tablet, twice a day. In patients in the ARAMIS study received a concurrent antiangiogenic therapy with r Pazopanib, which was stopped prematurely due to adverse events (AEs) after a median follow-up time of 6.1 months. AEs were increased in patients treated with NUBEQA compared to placebo. The most common AEs observed in patients treated with NUBEQA, including those resulting in discontinuation, were asthenia (15.4%), pain (7.7%), and fatigue (6.7%).

   Table 1 shows adverse reactions in ARAMIS reported to the FDA as of a 26% absolute increase in frequency compared to placebo. Table 2 shows laboratory tests abnormalities related to NUBEQA treatment and reported more frequently in NUBEQA-treated patients compared to placebo-treated patients in the ARAMIS study.

   **Table 1: Adverse Reactions in ARAMIS**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>NUBEQA (%)</th>
<th>Placebo (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>16</td>
<td>0.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Pain</td>
<td>4</td>
<td>0</td>
<td>0.2</td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
<td>0</td>
<td>0.1</td>
</tr>
</tbody>
</table>

5. **PREPARATION AND ADMINISTRATION**
   NUBEQA tablets are available as 160 mg and 320 mg tablets. The usual recommended dose is NUBEQA 160 mg twice daily. The dose should be decreased to NUBEQA 80 mg twice daily in patients with severe hepatic impairment (see Use in Specific Populations (8.5)).

6. **DRUG INTERACTIONS**
   7.1 Effect of Other Drugs on NUBEQA
   CYP3A4 inhibitors
   Concurrent use of NUBEQA with a CYP3A4 inhibitor decreases darolutamide exposure which may decrease NUBEQA activity (see Clinical Pharmacology (12.3)).

   CYP3A4 inducers
   Concurrent use of NUBEQA with a CYP3A4 inducer increases darolutamide exposure which may increase the risk of NUBEQA adverse reactions.

   7.2 Effects of NUBEQA on Other Drugs
   Breast Cancer Resistance Protein (BRCAP) and Ovarian X-linked Transporting Polypeptides (OATP) 1B1 and 1B3 Substrates
   NUBEQA is an inhibitor of BCRP transporters. Concurrent use of NUBEQA increases the AUC and Cmax of BCRP substrates (see 12.3) which may increase the risk of BCRP substrate related toxicity.

   7.3 Effects of NUBEQA on Laboratory Tests
   NUBEQA has no clinically relevant effects on laboratory blood tests (see Clinical Pharmacology (12.3)).

   8. **USE IN SPECIFIC POPULATIONS**
   8.1 Pregnancy
   NUBEQA has not been studied in pregnant women (see Use in Specific Populations (8.7, 8.8)).

   8.2 Lactation
   NUBEQA has not been studied in lactating women (see Use in Specific Populations (8.7, 8.8)).

   8.3 Females and Males of Reproductive Potential
   Contraception
   See Warnings and Precautions (5.1). The safety of NUBEQA has not been established in females. Based on its mechanism of action, NUBEQA can cause fetal harm and loss of pregnancy (see Clinical Pharmacology (12.3)). Animal embryofetal development studies were not conducted with darolutamide. There are no human data on the use of NUBEQA in pregnant females.

   8.4 Pediatric Use
   NUBEQA has not been studied in pediatric patients (see Use in Specific Populations (8.7, 8.8)).

   8.5 Renal Impairment
   NUBEQA is not recommended for patients with severe renal impairment (see Dosage and Administration (2.4)).

   8.6 Hepatic Impairment
   NUBEQA is not recommended for patients with severe hepatic impairment (see Dosage and Administration (2.4)).

   9. **OVERDOSAGE**
   There is no known specific antidote for darolutamide overdose. The highest dose of NUBEQA administered clinically was 900 mg taken daily, equivalent to a total daily dose of 180 mg. No dose limiting toxicities were observed with this dose.

   10. **PATIENT COUNSELING INFORMATION**
   Inform patients of the potential for NUBEQA to cause nausea, vomiting, diarrhea, constipation, and dry mouth. Inform patients that these effects may be dose-related, and may decrease with continued treatment. Inform patients to report these effects to their healthcare provider. The most common adverse reactions in patients treated with NUBEQA were asthenia (15.4%), pain (7.7%), and fatigue (6.7%).

   **References**

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How active surveillance has changed the management of prostate cancer

Q. Could you provide an overview of the development and uptake of active surveillance as a management strategy in prostate cancer?

WATTS: Active surveillance is a new approach to managing prostate cancer that arose in the beginning of the 2000s. But if you look back at what has happened with treatment for prostate cancer, it really traces all the way back to the early 1900s. In 1904, the very first radical perineal prostatectomy was performed at The Johns Hopkins Hospital. It wasn’t until 1945 that the radical retropubic approach was introduced by Terence Millin, MD.

Fast-forward almost 40 years, when the modified technique for radical prostatectomy was introduced by Patrick C. Walsh, MD. The goal of this was to reduce bleeding and avoid injury to the neurovascular bundle. Around this time, in the early 1980s, the [prostate-specific antigen] PSA blood test was discovered as a screening test for prostate cancer. In the late 1980s, the first template for the transrectal ultrasound-guided prostate biopsy was developed, so our ability to diagnose prostate cancer started to shift. At this point, all prostate cancers being diagnosed were being treated either with radical surgery—or radiation therapy.

Fifteen years or so later, in 2002, the very first report of active surveillance—it was called watchful waiting at the time—was published. It looked at the efficacy and use of active surveillance instead of actively treating a lot of these clinically localized, low-risk prostate cancers. This coincided with a lot of national data showing risks of the [adverse] effects associated with overtreatment, but the detrimental effects of both surgery and radiation, particularly for low-risk, clinically localized disease.

There have been several studies that have looked at the uptake of active surveillance after it was first introduced in 2002. It dramatically increased mostly in the past 2 decades but particularly after 2010. An analysis in the United States from the [Surveillance, Epidemiology, and End Results] SEER database looked at data from 2010 to 2015, and, across the United States, the rate of uptake in active surveillance went from single digits for low-risk disease to 40% to 50% on average. But what also emerged from this [and] other analyses was that there is considerable variation in uptake by geographic region in the United States.
States, [as well as] other factors, such as ethnic group [and] socioeconomic status.

Beyond our national variation, there’s also been a lot of variation by country in terms of the uptake and use of active surveillance. There are data from an analysis in Sweden examining the rates of active surveillance uptake for men with variable-risk disease, from the inception of active surveillance to a 6-year follow-up. The rates of active surveillance in Sweden went to 91% across the country for men with very low-risk disease, 74% for those with low-risk disease, and even up to 19% for those with intermediate-risk disease. Our country has certainly had a boom in the adoption and uptake of active surveillance, but even with that, we lag behind some European countries. Sweden is 1 example, but there are quite a few others that also have very high rates of uptake of active surveillance.

The other point I would make is that in addition to the uptake and the widespread use of active surveillance for men with low-risk disease, a lot of our national organizations have guidelines supporting the use of this. Our own American Urological Association guidelines from 2017 gave a grade A, which is a strong recommendation that active surveillance should be recommended as the best available care option for men who have very low-risk disease and the preferable option for those with low-risk disease. This is a complete change from what we were doing even just 20 years ago.

In addition, the [National Comprehensive Cancer Network] NCCN also has been very much supporting this for the past decade. A lot of people reading this are probably aware of the social media explosion that happened in September 2021. Just a few months ago, the NCCN changed their recommendation of active surveillance as the preferred or standard option for low-risk disease to state that it was no longer indicated as the preferred treatment for this group of men. Almost overnight, this sparked an outcry among urologists and investigators, and it blew up on Twitter. As a result, in December, the committee reconvened and updated their statement, again, to indicate that men with low-risk disease should be offered active surveillance as the only preferred treatment strategy. This is a tremendous difference and advancement compared [with] what we were doing 20 years ago, and certainly in the [past] 50 years if we’re looking at how we’ve been treating and approaching prostate cancer.

Q. How has your own clinical practice evolved regarding application of active surveillance protocols?

WATTS: My practice is in the Bronx, New York. We work in a demographic with men from very low socioeconomic—status backgrounds and an extremely heterogeneous population—very ethnically diverse, at least 50% Black and/or Hispanic men. English is not the predominant language spoken in the boroughs, where we treat our patients. We [must] be mindful of some of these other factors that we know nationally affect implementation of active surveillance protocols. [Despite] this, the overall rates of using active surveillance by our faculty have more than doubled for the appropriate candidates in the past 5 years, and even more so if you look back 10 years.

When I look at what we were doing from a protocol standpoint—when active surveillance was first being implemented here over a decade ago—we were just using follow-up PSAs and biopsies when indicated and occasionally incorporating MRI prostate for imaging follow-up. But now that we know that the emergence of data supporting MRI prostate, ultrasound, fusion-guided prostate biopsies, and incorporating fusion biopsies into surveillance protocols, we have incorporated that in the initial diagnostic front [and] in our surveillance follow-up for men for over 5 years now. We also have developed the concept of an adaptive active surveillance protocol, because not every man and not every cancer is the same—so being a little adaptive in terms of the individual patient parameters, the risk factors, their family history, ethnicity, and clinical variables.

“Active surveillance is an innovation because it’s truly a departure from the idea that all prostate cancers or cancer in general needs to be treated.”

KARA L. WATTS, MD
Robotic cystectomy is effective, but clinical impact is uncertain

Radical cystectomy, along with systemic therapy, remains the recommended standard of care for patients with muscle-invasive bladder cancer. Several interventions have been utilized to improve the outcomes following radical cystectomy. These include subspecialization, regionalization, early recovery protocols, and more recently, use of minimally invasive robotic surgery.

To determine the effect of robotic surgery on perioperative recovery and complications, Catto et al conducted a randomized controlled trial comparing completely intracorporeal robotic cystectomy with open surgery.1 The primary outcome measure was the number of days alive and out of the hospital within 90 days of surgery. Several other secondary outcomes were measured, including complication rate, quality of life, activity levels, and survival.

The investigators randomized 338 patients to either robotic radical cystectomy with intracorporeal reconstruction or open radical cystectomy. Of these, 317 patients underwent radical cystectomy and 305 were analyzed for primary outcome after either robotic radical cystectomy (n = 156) or open surgery (n = 149). Nearly one-third of patients received neoadjuvant chemotherapy and 89% received an ileal conduit.

The authors report that the median number of days alive and out of the hospital within 90 days of surgery for patients undergoing robotic cystectomy vs open surgery was 82 days and 80 days (P = .01), respectively. The median length of hospital stay was 7 days for robotic cystectomy and 8 days for open surgery (P = .05). Hospital readmission after discharge was required in 21.8% undergoing robotic cystectomy and 32.2% undergoing open cystectomy (difference, 10.4% [95% CI, 0.5%-20.3%]; P = .04). Cancer recurrence rates and all-cause mortality were similar between the groups.

Two-thirds (65.6%) of the patients had at least 1 complication within 12 weeks, including 63.4% in the robotic surgery group and 67.9% in the open surgery group. The robotic surgery group, compared with open surgery, had significantly fewer wound-related complications (5.6% vs 17.3%; difference, −11.72%) and thromboembolic complications (1.9% vs 8.3%; difference, −6.47%).

General health-related quality of life (HRQOL) at 5 weeks was statistically significantly worse in the open surgery group, but the scores were similar between the groups at 12 weeks. Using a different HRQOL instrument, statistically significantly higher HRQOL was noted in the robotic surgery group at 5 and 12 weeks, but no difference was noted by 26 weeks. This randomized controlled trial (RCT) has some important and distinct features when compared with previous studies. The current study focused on postoperative recovery, including complications and readmission using a completely intracorporeal technique. A previous RCT comparing robotic surgery (with open diversion) and open surgery had primarily focused on oncological outcomes, declaring the robotic approach as noninferior.2 The current study used an interesting primary endpoint (ie, number of days alive and out of hospital), which is a composite of postoperative length of stay, any readmissions, and deaths within 90 days. The investigators used 2 days as the minimum detectable difference for robotic surgery, as this difference was viewed by their health care purchasers to be of sufficient benefit to fund robotic surgery service in the British health care system. This difference of 2 days over a 3-month period may be too modest to mitigate the health care cost of robotic surgery in the United States.

Much of the benefit from robotic or other minimally invasive approaches is realized in the early postoperative period as evident from the early convalescence, increased mobility, and improved HRQOL in the first 5 weeks after surgery. However, the differences in HRQOL and activity level disappeared by 3 or 6 months after surgery.

The investigators are to be commended for being able to conduct an RCT of 2 surgical approaches—a task that has been notoriously difficult to complete. This study demonstrated that robotic cystectomy with intracorporeal diversion was statistically superior by 2 days in terms of days alive and out of the hospital. As the authors point out, the clinical importance of these findings across various health systems and patient populations is uncertain.

Other studies have reported that proposed benefits of robotic surgery, such as smaller incisions, improved high-definition vision, decreased blood loss, and increased mobility, may not translate into improved functional recovery, HRQOL, or cancer control. Yet, several high-volume centers continue to promote the use of the robotic approach as the new standard of care. With the relatively modest and variable advantages of robotic cystectomy reported by this and previous RCTs, surgeons should continue to offer their best surgical technique (open or robotic) to patients.
The lockdown of more than 26 million individuals in Shanghai, China, on March 31, 2022, following a spike in COVID-19 cases impacted GE Healthcare’s primary pharmaceutical manufacturing facility for iohexol (Omnipaque) iodinated contrast media (ICM). As of mid-May 2022, the FDA continues to report shortages of GE Healthcare’s iohexol and iodixanol intravenous (IV) contrast media products. GE Healthcare anticipates product supply availability to improve the week of May 23, but a 20% allocation level has been established until then.

The acute shortages impacting hospitals and imaging centers globally have emphasized the importance of judicious resource allocation. The evaluation of microscopic hematuria (MH) is particularly relevant to examine in this setting, based on both its prevalence (variously estimated to occur in 6.5% of the population) and the fact that the diagnostic evaluation for hematuria has historically been heavily weighted to the use of CT imaging with ioxixanol IV contrast. Indeed, prior guideline recommendations have essentially suggested CT urogram (CTU) with cystoscopy as the evaluation for all patients with microhematuria who are older than 35 years.

Notably, the updated 2020 American Urological Association (AU/A)/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) guidelines for MH help to address the issue of contrast utilization by both providing a risk-stratified approach based on likelihood for harboring malignancy—whereby IV contrast–based CTU is recommended only for high-risk patients—and by outlining alternative modalities to the imaging evaluation. Specifically, risk strata were created based on clinical features, including patient age, gender, smoking history, extent of hematuria on urinalysis (UA), and history of risk factors for urothelial cancer (eg, exposures). In patients with MH classified as low-risk, the guidelines recommend clinicians should engage patients in shared decision-making to decide between either repeating a UA within 6 months and proceeding with cystoscopy and renal ultrasound. Meanwhile, for patients classified as intermediate risk of malignancy, the guidelines offer cystoscopy with renal ultrasound for evaluation. As such, the use of multiphasic CTU, which utilizes ICM and includes imaging of the urothelium, to evaluate MH is recommended by the new guidelines only for high-risk patients.

This risk-based approach for MH evaluation represents 1 important step the medical/urologic community can adopt to restrict IV contrast utilization. These recommendations were based on the balance of risks and benefits, as CTU has additional cost and toxicity relative to renal ultrasound and a relatively small yield of identifying malignancy, especially in low- and intermediate-risk patients, where the incidence of upper tract malignancy is very low. Further, the guidelines offer that for patients in the high-risk category, magnetic resonance urography (MRU) may be utilized to image the upper urinary tract, which would provide an alternative to utilizing CT IV contrast.

Data on the performance of imaging with noncontrast CT, MRU, and renal ultrasound were collated as part of the analysis for the AUA/SUFU guidelines. Because all modalities are quite sensitive for detection of renal cortical...
tumors—most of which are renal cell carcinoma (RCC)—the comparisons among modalities focused on performance characteristics for detection of upper tract urothelial carcinoma (UTUC), which is a relatively rare finding in patients with microhematuria.

The current gold standard for upper tract imaging is CTU. Four studies identified by the systematic review underpinning the guidelines reported on the diagnostic test characteristics of CTU for the detection of UTUC and RCC in a hematuria population.4-7

Based on pooling of the 6 sensitivities and specificities in the 4 studies, the pooled sensitivity for CTU detection of UTUC or RCC was 94.16% (95% CI, 83.77%-98.05%) and the specificity was 99.09% (95% CI, 96.59%-99.76%).4-7

Only 1 study reported on the diagnostic ability of nonenhanced CT for UTUC detection in solely MH patients.4 The study defined pathologic confirmation of malignancy as the reference standard. In patients who underwent CTU for initial evaluation of asymptomatic MH, the noncontrast images of a randomized portion of the cases was categorized as normal, and all cases categorized as suspicious and benign were submitted to 2 blinded radiologists who independently classified each study into 1 of the aforementioned categories. When compared with the CTU reports, the negative predictive values of noncontrast images were 97.25% and 94.92% for radiologist 1 and radiologist 2, respectively, with an associated specificity of 88.6% and 97.95%. Of the 5 true upper tract malignancies, both blinded radiologists correctly identified 4 of the 5.

Two studies reported on the diagnostic test characteristics of ultrasound for the detection of UTUC and RCC.5,6 Tan et al reported on detection of both UTUC and RCC, whereas Unsal et al reported on detection of only UTUC.2 Both studies defined pathologic confirmation of malignancy as the reference standard. In the Tan et al study, the sensitivity for RCC was 85.7% (95% CI, 62.1%-97.5%) with a specificity of 99.2% (95% CI, 98.8%-99.5%), but the sensitivity for UTUC was low at 14.3% (95% CI, 0.9%-49.4%).5 The Unsal et al study had a much higher sensitivity for UTUC of 96%, with specificity of 100%.8

One study reported on the diagnostic test characteristics of MRU for the detection of neoplastic lesions in patients with MH or gross hematuria.6 Martingano et al defined pathologic confirmation of malignancy as the reference standard. In this study, the sensitivity for RCC or UTUC was 83% and specificity was 86% based on review by 2 radiologists.6

Although there is not a considerable amount of data, there are other options for use of oral ICM, such as sorbitol-mannitol-xanthan gum (Breeze; Beekley Medical) and diatrizoate meglumine and diatrizoate sodium solution USP (Gastrografin; Bracco Diagnostics Inc).6 Similarly, sorbitol-mannitol-xanthan gum and iothalamate meglumine (Cysto-Conray; Guerbet LLC) can be used for cystography, retrograde urography, as well as for percutaneous renal access and nephrostomy procedures.9

**SUMMARY AND RECOMMENDATIONS**

The global shortage of ICM has necessitated rapid adaptation of workflows and clinical pathways, which are particularly important for practicing urologists who are evaluating patients for hematuria. Based on the meta-analyses for the AUA/SUFU guidelines7 for evaluation of microhematuria, CTU has the highest sensitivity for detection of UTUC compared with unenhanced CT, MRU, and renal ultrasound. However, given the rarity of UTUC11—particularly in the setting of the current shortage of ICM—we believe the risk-stratified approach to evaluation, as recommended in the 2020 guidelines, offers appropriate resource conservation. Indeed, to review:

- For patients with low-risk microhematuria undergoing evaluation, consider shared decision-making for a period of observation with repeat UA, or evaluate with a cystoscopy and renal ultrasound. For patients with intermediate-risk microhematuria, cystoscopy with renal ultrasound is recommended.1

- For patients with high-risk microhematuria, the guidelines do recommend CTU. However, the authors believe that in the setting of ICM shortage, a tiered approach may be considered, with initial renal ultrasound or noncontrast CT with subsequent CTU for those with abnormal findings. Importantly, MRU represents an alternative modality to evaluate high-risk patients, albeit with potential cost and access implications.

- Patients with gross (macroscopic) hematuria are at highest risk for receiving a diagnosis of a urologic malignancy among patients with hematuria. These patients should be prioritized for CTU, again, with the option of using MRU as the initial imaging study, pending local ICM availability.

Other mitigation strategies for urology patients include the following:

- Consult with local radiology colleagues to discuss use of alternative contrast agents for cystography, retrograde urography, and for percutaneous renal access and nephrostomy procedures.

- Delay routine cancer surveillance imaging or utilizing MR-based imaging for cancer follow-up as available/appropriate.

- Use MRI with and without contrast to delineate and stage renal cortical tumors.

The authors recognize that ICM is also relevant in multiple other clinical settings urologists manage, including new cancer diagnosis staging, and evaluation of suspected perioperative complications. Thus, in addition to monitoring supplies of ICM, the leadership team must also monitor availability of the alternative imaging strategies, as large-scale diversion of contrasted CT into MRI and ultrasound could lead to resource shortages in those areas. Such alternatives include delaying the timing of CTs requiring IV contrast and employing lower-dose regimens when ICM is necessary. It is critical for urologists to communicate with their radiology colleagues, pharmacy colleagues, and administrative leaders to form a local strategy for conserving supplies while still delivering the highest-quality care available.

A comprehensive plan would include designating a leadership team with all relevant disciplines represented; gathering information, such as local supply of ICM and local availability of alternative imaging options; establishing clinical protocols to prioritize use of ICM in crucial scenarios while conserving its use in others; and establishing a communication plan to disseminate the information. A recent study highlights some short-, mid-, and long-term strategies to manage the shortage of iohexol.10

### Cover Feature

Urologists in cancer care

https://bit.ly/3ah2qZv

To view the full reference list, scan the QR code or visit https://bit.ly/3ah2qZv
Roundtable discussion: Strategies for prostate cancer screening

**Urology Times®** Case-Based Roundtable program encompasses peer-to-peer discussion of clinical cases. This case discussion involves a 65-year-old man who is referred to a urologist by his primary care provider with a prostate-specific antigen (PSA) level that has increased from 2 ng/mL to 4.1 ng/mL. The patient is otherwise fine and is not aware of any family history of prostate cancer.

**PUNNEN:** What would your next step be for this patient?

**CHANG:** I would use a free PSA before the biomarkers. It’s cheaper.

**PUNNEN:** Would there have been a particular cut point you would’ve used to do anything further?

**CHANG:** If it’s less than 10%, I would probably either order a biopsy or if I can’t get an MRI, I would move to a biopsy. I go for the MRI first and then go from there. If it’s above 25%, I would sit tight. If it’s equivocal, then we have to have a discussion.

**PUNNEN:** In this particular situation, the urologist recommended MRI, but the patient was reluctant and had some transportation issues and didn’t want to come in for the MRI. What would you do at this point? Would you do a biopsy? Would you just watch the PSA?

**ADLER:** I would have a goals discussion with this patient and just go over the data with them. I have a lot of these conversations with patients. What do they expect? What do they want to do? Particularly in patients who are in their 70s, we’ll go over their health. If they’re otherwise healthy, then I will tell them we can do further testing or we can just watch the PSA, bring them back in 3 to 6 months, and then go from there. Once in a while, I’ll have someone ask me, “Why are we waiting that long to repeat my PSA?” My answer at that point is, “We need to go ahead and do further testing because if you don’t feel comfortable watching, then you want to do something.” I don’t have a knee-jerk approach to doing this. I want to understand how comfortable they feel and so on and so forth. Then we can go from there with the understanding that anything we hold off on doing now, we can certainly do in the future.

**PUNNEN:** In this particular situation, the patient did get a biomarker just because he didn’t want to come for the MRI. In this case, if you’re thinking about biomarkers, what factors may make you decide on one biomarker over another?

**CHADWELL:** For me, it mostly boils down to access in terms of what’s easy for me to have the patient do and what will be covered by the majority of the insurances.

**ADLER:** I agree with that last statement. A lot of patients are on 5-α-reductase inhibitors, so that throws 4Kscore right out the window. Plus, if the patient has had any procedure recently—if you did a cystoscopy for a microhematuria assessment at the same time, if you haven’t done the 4Kscore at that point, you can’t get it for another 6 months because they haven’t validated it for the impact of procedures. Plus, at least locally, you have to counsel the patient about potential cost. That’s important. ExosomeDX is something we’ve been using a lot of recently because even if we did a recent digital rectal exam, then we can have a kit sent to the patient’s house and it’s a very easy, very efficient process. I think that’s where we are right now. Unfortunately, the Prostate Health Index is not available in our state due to licensing issues, so we can’t get it.

**PUNNEN:** Given this patient’s transportation issues, he preferred the at-home ExosomeDx test. His result is 47.4, which gives him a 45% risk for high-grade cancer. What would be your next step? Would you do a biopsy, or is it more to target a biopsy?

**KHAN:** [I would have an MRI done ahead of a] targeted biopsy. He needs a biopsy…so that’s where you want to do MRI—so you can do a targeted biopsy.

**GLASER:** For me, it’s for both.
ADLER: Depending upon the community you're in, you're almost obligated to get the MRI. If you do a biopsy and find no cancer, [atypical small acinar proliferation], or high-grade [prostatic intraepithelial neoplasia], and you have not done an MRI initially, now you're doing an MRI on the patient afterward. If you find something on there that's suspicious, now you're telling the patient they need a second biopsy as a fusion biopsy. The patient is going to want to know why the MRI wasn’t done in the first place to allow for an up-front fusion biopsy.

GORIN: I agree; you end up chasing your tail if you don’t start with an MRI just the way Dr Adler outlined.

KHAN: Some patients say they don’t want an MRI. Would you just go ahead and do the regular mapping biopsy? Sometimes, the insurance doesn’t approve and sometimes patients say they don’t want MRI; they just want the biopsy. Would you do the biopsy without MRI?

PUNNEN: I think you have those discussions with your patient. I do feel like it’s the minority who won’t get the MRI because I feel like most of them are already coming in saying, “I don’t want a blinded biopsy.” They want something to direct it. Let’s say we have this scenario. Most of us agreed that we would get the MRI. The MRI comes back negative. Would that change what you do now? Would you say, “OK, we don’t need a biopsy,” or would you do anything differently? Would you get another test to break the deadlock?

GORIN: In this case, I feel the necessity for a biopsy has already been established on the basis of the ExosomeDx test. The only reason to have ordered an MRI was to determine whether there is anything to target at the time of biopsy.

PUNNEN: Would anyone have done anything different? I share Dr Gorin’s views. In this particular patient, they did end up going on with the biopsy and he was found to have grade group 4 cancer. When we think about where we used to be with just PSA as a marker and having some of the derivatives if the PSA came into this critical area, do you feel like MRIs and liquid biomarkers have addressed the unmet need in this space? Is there still an unmet need? What are your thoughts on research that needs to be done to help us better?

ADLER: There’s actually one test I would love to see come about. I had the opportunity to help an investigator look at urinary telomerase years ago. It was a small study, but we had a negative predictive value of 100%. If you had a negative urinary telomerase, you did not have prostate cancer. It was a guarantee. Then, in the positive group, we had a very high positive predictive value, and 2 patients in the study had slightly elevated results. Initial biopsies were negative, but about 2 to 3 years later they had follow-up biopsies and were found to have significant cancer. That was outside of this trial that we had done. Unfortunately, she wasn’t able to take this research any further. That’s a test with which I would feel comfortable telling a patient whether they needed a biopsy.
Conference Highlights | AUA

INTEGRATING IS ASSOCIATED WITH TUMOR REDUCTION IN PATIENTS

Localized upper tract urothelial carcinoma (UTUC) treatment with infgratinib (Truseltiq) was associated with tumor reduction, ranging from 25% to 83% in 44% of patients evaluated, investigators report. The interim results from a biomarker-informed preoperative study of infgratinib, an oral inhibitor of FGFR1 to FGFR3, demonstrated substantial activity and tolerability in patients with localized UTUC, according to findings of a phase 1b trial (NCT04228042).

A total of 12 patients with FGFR3 mutations were enrolled, with 11 patients deemed evaluable, according to investigators. Nine patients completed therapy and 2 continued on treatment as of the data cutoff. However, 2 patients experienced toxicities that resulted in dose reductions and 2 patients discontinued treatment. One patient discontinued treatment because of fatigue and 1 patient discontinued because of liver injury. Four of 9 patients (44%) who completed therapy showed tumor reduction that ranged from 25% to 83%. From a clinical perspective, 2 patients who were scheduled to undergo nephroureterectomy were able to be treated through endoscopic management.

Surena F. Matin, MD, the Monteleone Family Foundation Distinguished Professor with Tenure in the Department of Urology at The University of Texas MD Anderson Cancer Center in Houston, presented the findings. Investigators reported that all responders had FGFR3 mutations and that most nonresponders had a prior history of bladder cancer, with 1 patient having a FGFR3-TACC3 fusion. Four patients who were biomarker negative did not have a response.

Patients with low-grade or localized cisplatin-ineligible, high-grade UTUC who were candidates for either ureteroscopic (URS) management or nephroureterectomy/ureterectomy (NU/U) were enrolled from May 2021 to February 2022. Eligibility requirements included having a glomerular filtration rate of 30 or greater, sufficient biopsy tissue that could be used for mutational analysis, and a tumor map for residual tumors after biopsy and ablation. Patients were ineligible if they had a primary malignancy within 3 years, had uncontrolled bladder cancer, or had impaired gastrointestinal function that affects the absorption of oral infgratinib.

Patients received 2 cycles of 125 mg of oral infgratinib for 21 days of a 28-day cycle. After completing the second cycle, patients underwent tumor mapping based on URS or NU/U. The primary end point was tolerability, and the secondary end points were objective response based on tumor mapping, circulating cell-free DNA analysis, expression of markers, and FGFR3 alteration type. Targeted sequencing...
was conducted using a NovaSeq 6000 solid tumor panel accounting for 610 somatic alterations, including 33 fusions.

ANTEGRADE INSTILLATION OF MITOMYCIN GEL IS EFFECTIVE IN UTUC
Mitomycin gel (Jelmyto) can be safely and effectively administered through antegrade instillation to patients with low-grade upper tract urothelial cancer (UTUC), according to a retrospective review of real-world data. Administration of mitomycin gel via retrograde administration using a ureteral catheter is more widely used than antegrade administration via percutaneous nephrostomy tube. For example, all evaluable patients in the pivotal OLYMPUS trial (NCT02793128) received 6 once-weekly treatments via a retrograde approach.\(^3\)

Investigators noted that patients required general anesthesia for the procedure, which may correlate with an increased cost and morbidity. Additionally, repeat procedures via catheter may be a contributing factor to the development of ureteral stenosis.

Mitomycin gel was approved for either antegrade or retrograde administration in 2020 based on data from the phase 3, single-arm OLYMPUS study.\(^4\) To circumvent the associated complications with retrograde administration, investigators pooled data from multiple institutions, at which patients received mitomycin gel via antegrade administration. All patients underwent induction therapy of 6 once-weekly administrations of mitomycin gel, administered using percutaneous nephrostomy tube.\(^5\)

The retrospective analysis identified 26 patients who received treatment across 4 institutions. In terms of efficacy, 50% of patients had a complete response (CR) and 46% had a partial response at postinduction ureteroscopy, with 1 patient experiencing progression to invasive disease. Further, at a median follow-up of 7 months, no patients with a CR experienced disease recurrence.\(^2\)

In an analysis of the safety data, no patients reported impaired renal function during the follow-up period, and 15% of patients reported ureteral stenosis. Other adverse effects included fatigue (27%), flank pain (19%), urinary tract infection (12%), sepsis (8%), and hematuria (8%). No patients died on treatment. Nine patients (35%) received at least 1 dose of maintenance therapy with mitomycin gel, and 6 patients (23%) in the retrospective analysis had solitary kidneys.\(^2\)

NEOADJUVANT CHEMOIMMUNOTHERAPY SHOWS PROMISE IN MIBC
Initial data from the phase 2 TRUCE-01 trial showed that the neoadjuvant combination of the PD-1 inhibitor tislelizumab and nab-paclitaxel (Abraxane) induced a high rate of pathologic complete response (pCR) in patients with muscle-invasive bladder cancer (MIBC).\(^5\)

Investigators of the single-arm, open-label phase 2 trial (NCT04730219) did not observe an increase in adverse events (AEs) or a cor-
relation of PD-L1 expression with the efficacy of the neoadjuvant therapy. However, high tumor mutation burden (TMB) did show a correlation to response with the combination.

Neoadjuvant treatment with immune checkpoint inhibitors showed comparable efficacy and fewer AEs than chemotherapy in the PURE-01 trial (NCT02736266) of pembrolizumab (Keytruda) and the ABACUS trial (NCT02662309) of atezolizumab (Tecentriq) in MIBC. Although, at this point, the efficacy of combination chemotherapy and PD-1/PD-L1 inhibition has not been determined. This study in patients with MIBC is evaluating the PD-1 inhibitor tislelizumab combined with second-line chemotherapy in the neoadjuvant setting.

In the ongoing TRUCE-01 trial, patients with stage T2-4aN0-M0 disease were given 200 mg of tislelizumab on day 1 and 200 mg of nab-paclitaxel on day 2 every 3 weeks for 3 cycles, followed by complete transurethral resection of bladder tumor (cTURBT) or radical cystectomy. The Dako 22C3 pharmDx assay was used to conduct biomarker analysis on PD-L1 expression using combined positive score. TMB was also evaluated for the analysis. The primary end point was pCR, defined as the absence of a viable tumor (pT0N0M0).

Thirty patients completed this regimen of neoadjuvant tislelizumab plus nab-paclitaxel and received a radical cystectomy (n = 9) or cTURBT (n = 21) between July 2020 and July 2021. A total of 16 patients achieved pCR (53.3%; 95% CI, 36.7%-73.3%). Downstaging to pT less than 2 occurred in 21 patients (70%; 95% CI, 53.3%-86.7%), which was a secondary end point in this trial.

Patients who responded to therapy had a higher TMB level than those who did not respond (P = .067). No significant correlation was observed between PD-L1 expression and the efficacy of the tislelizumab/nab-paclitaxel combination. Eight patients with PD-L1-positive expression achieved pT0 versus 8 patients with PD-L1-negative expression (P = .484).

In terms of AEs, 1 patient experienced grade 3 rash and 1 patient had grade 4 acute renal failure. After corticosteroid treatment, both patients recovered. The most common grade 1 or 2 AEs were alopecia, observed in 96% of patients, fatigue in 63%, hyperglycemia in 33%, rash in 27%, fever in 17%, and creatinine increase in 13%.

The change in average IPSS from baseline to follow-up was –8.88±8.96, –10.31±5.07, and –9.60±6.69, for the 50-59 months, 60-71 months, and 72-79 months groups, respectively. These numeric changes translated to percent changes of 41.0%, 54.6%, and 50.3%, respectively (P < .0001 for all).

The change in average IPSS-QoL score was –2.04±1.81, –1.85±1.52, and –1.80±0.84, respectively. These numeric changes translated to percentage changes of 46.8% (P < .0001), 43.8% (P < .0001), and 51.3% (P < .0015), respectively.

Regarding safety, there were no patients who had late postoperative complications.

REFERENCES

For all of Urology Times’ coverage of this meeting, scan the QR code or visit https://bit.ly/3yo8ozp

For all of Urology Times’ coverage of this meeting, scan the QR code or visit https://bit.ly/3yo8ozp
AUA 2022 features updates on darolutamide, relugolix, N-803

**BLADDER CANCER**

Joshua J. Meeks, MD, PhD | Associate professor of urology, Northwestern University Feinberg School of Medicine, Chicago, Illinois

Abstract PLLBA-01: Final clinical results of pivotal trial of IL-15Rα superagonist N-803 with BCG in BCG-unresponsive CIS and papillary non–muscle-invasive bladder cancer: “A lot of us are very interested in seeing the real data from this paper...in manuscript form, mostly because the tolerability was very, very good. In fact, they reported no grade 4 or 5 [adverse events] and really minimal toxicity. It’s hard to believe that it does that well when it’s given with BCG, because all of us—as providers who take care of patients with BCG—see a certain amount of toxicity just with standard BCG. So, the thought of adding to that, [and] it seems to be better than BCG alone—it’s hard to say whether that’s how it’s reported or there’s actually an improvement in symptoms. We all kind of think that when BCG doesn’t work in patients, it’s because they don’t have symptoms, suggesting there’s not enough inflammation.

There certainly seems to be a correlation where the more symptoms people have, the longer disease-free survival they have. So in this case, they don’t have symptoms, but they have a pretty good disease-free survival. Again, I’ll be really excited to see the manuscript written up so we can really look at it, but this is probably some of the most exciting work I’ve seen in bladder cancer in a very long period of time.”

**PROSTATE CANCER**

Ashley E. Ross, MD, PhD | Associate professor of urology, Northwestern University Feinberg School of Medicine, Chicago, Illinois

Abstract LBA01-07: Overall safety and incidences of adverse events by time interval with darolutamide plus androgen-deprivation therapy and docetaxel in the phase 3 ARASENS trial: “The take-homes here are 2-fold. First, for sure, you should not be doing androgen deprivation therapy [ADT] alone in [men with] newly diagnosed metastatic hormone-sensitive prostate cancer, or at least it should be your second consideration....Second, darolutamide [Nubeqa], perhaps because of its unique chemical structure and its toxicity profile, does not add extra morbidity in this setting. So, for your [healthy] chemotherapy-eligible patients who have high-volume or otherwise high-risk disease, we really should be thinking about trimodal therapy with darolutamide and docetaxel as well as ADT.”

Abstract MP27-16: Oral relugolix for androgen deprivation therapy in advanced prostate cancer: detailed safety analysis from the randomized phase 3 HERO study: “This looked at details of the safety analysis from the HERO trial [NCT03085095], so it was studying adverse events [AEs] when using relugolix. [The authors reported] very similar AEs [when] comparing relugolix with leuprolide. It was interesting to see [that] they broke down the AEs by when they would start in the man and how long they would last on median....Overall, it solidified that relugolix is an extremely well-tolerated drug without really appreciable excessive toxicities compared with leuprolide.”

**PENILE/TESTIS/RARE CANCERS**

Philippe Spiess, MD, MS | Genitourinary oncologist and the assistant chief of surgical services at Moffitt Cancer Center, Tampa, Florida

“If you look specifically at testicular cancer, areas of focus right now include patients who have certain types of tumors, particularly seminomas; [these are] low-volume tumors in the retroperitoneum, typically stage IIA tumors. There are some emerging data from both Germany and from a group from [the University of Southern California, Los Angeles] showing that primary surgical resection seems to be a very feasible treatment approach vs what we would typically do in most of these patients, with really excellent outcomes and really low surgical morbidity. They’re really highlighting a new treatment paradigm for low-volume seminoma cancer. There were also a few presentations from several groups internationally in a nonseminoma setting, revisiting predicting histology of tumors, in terms of prior to resection, to try to see ultimately if we could avoid doing surgical resection in some patients. Some of the work showed that our clinical models are improving [in terms of] predicting histology, but I don’t think that we’re at the point where we could stop doing surgical resection, unfortunately, in many patients who have masses after chemotherapy.

“In penile cancer, a couple of presentations looked at having a better appreciation of sentinel lymph node biopsy: how it can be performed, getting excellent results. A large number of institutions in the United Kingdom have adopted doing dynamic sentinel lymph node biopsy vs doing surgical resection; it seems like it’s really a very valid, appropriate, and reproducible tool. What is clear, though, is that it’s very operator and volume dependent. You have to perform a certain amount of these cases to get the necessary refinement in terms of diagnostic utility, high sensitivity and specificity, and low negative predictive value.”
Ethnic differences in men undergoing reproductive urology evaluation

Although up to 50% of infertility cases have a male factor component, there are scant data on what factors are associated with the male partner undergoing a fertility evaluation. Racial differences in fertility care have been identified, most from the National Survey of Family Growth (NSFG), which evaluates the American civilian population. Data from the 2011-2017 NSFG found that 9.5% of men seeking infertile services were Black, 69.1% were White, 16.1% were Hispanic, and 5.3% identified as “other.” Black women have been shown to have a 1.45 times greater adjusted prevalence of infertility compared with White women. Lastly, Black men are more likely to have their female partner undergo testing first, as compared with White men.

In a multi-institutional survey-based publication of men in North America undergoing fertility evaluation by a reproductive urologist, several key racial differences were identified. The racial breakdown of 6462 men was: 51% White, 20% Asian/Indo-Canadian/Indo-American, 6% Black, 1% Indian/Native, fewer than 1% Native Hawaiian/Other Pacific Islander, and 21% other. The following differences were seen:

- White men sought evaluation sooner after initiating paternity attempts (3.5 ± 4.7 years vs 3.8 ± 4.2 years), had older female partners (33.3 ± 4.9 years vs 32.9 ± 5.2 years), and more had undergone vasectomy (8.4% vs 2.9%) vs all other races.
- Black men were older (38.0 ± 8.1 years vs 36.5 ± 7.4 years) and sought fertility evaluation after initiating paternity attempts (4.8 ± 5.1 years vs 3.6 ± 4.4 years), fewer had undergone vasectomy (3.3% vs 5.9%), and fewer had partners undergo intrauterine insemination (8.2% vs 12.6%).
- Asian/Indo-Canadian/Indo-American men were younger (36.1 ± 7.2 years vs 36.7 ± 7.6 years), fewer had undergone vasectomy (1.2% vs 6.9%), and more had partners who underwent intrauterine insemination (14.2% vs 11.9%).
- Indian/Native men sought evaluation later (5.1 ± 6.8 years vs 3.6 ± 4.4 years) and more had undergone vasectomy (13.4% vs 5.7%).

With respect to lifestyle factors:
- White men were more likely to be overweight (defined as body mass index [BMI] ≥ 25.0 kg/m²) or obese (as defined by BMI ≥ 30.0 kg/m²) when compared with all other races (74.4% vs 69.5%).
- White men were more likely to drink alcohol (84.7% vs 73.6%).
- White and Indian/Native men were more likely to use marijuana (20.1% vs 13.0% and 28.4% vs 16.5%, respectively).
- White men were more likely to report cocaine use (1.9% vs 1.2%).
- White men were more likely to have used steroids (1.3% vs 0.6%) and exogenous testosterone, as compared with other populations (1.3% vs 0.6%).

Prior studies show that assisted reproductive technology usage rates among Black, non-Hispanic women are lower than the average US utilization rate and White women are more likely to utilize fertility services. One of the clearest examples of racial differences on reproductive choices that we identified was in vasectomy rates. Asian/Indo-Canadian/Indo-American and Black subgroups were less likely, whereas White and Indian/Native subgroups were more likely to have had a vasectomy as compared with other races. This is similar to data from the 2002 NSFG, which found that Black and Hispanic men were less likely to rely on vasectomy for contraception, even after accounting for a host of other factors (14.1% of White men, 3.7% of Black men, and 4.5% of Hispanic men had a vasectomy). Willingness to undergo medical investigation and therapy may also be affected by social and cultural backgrounds. Black patients have been shown to report lower levels of trust in health care providers when compared with White patients, often related to a history of lower quality interactions with health care providers. And although racial differences in patient’s medical care preferences may exist, racial differences in referral patterns and decisions to initiate treatment may remain.

Racial differences exist for men undergoing fertility evaluation by a reproductive urologist. These differences, such as age, duration of infertility, previous vasectomies, partner age, BMI, lifestyle factors, and previous reproductive outcomes, may be due to a variety of differences between racial groups. As clinicians, we must better understand how race plays a role in fertility therapy. The associations between race, biologic, and societal factors in fertility should guide clinicians as they obtain a history, counsel patients, and expand outreach to underserved populations. Increased awareness is a critical step in addressing inequities and disparities in infertility.
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What to know about billing for unlisted codes

Supplemental information on safety and efficacy of service may be needed

Q. I am having issues billing an unlisted code for a new procedure the doctor is performing. Do you have any suggestions for appropriate billing of an unlisted code?

A. Unlisted codes are not unfamiliar to urology practices. According to Current Procedural Terminology (CPT) coding instructions, when procedures or services performed by physicians do not have a valid or descriptive CPT or Healthcare Common Procedure Coding System (HCPCS) code, the service should be reported using an unlisted code. The unlisted code selected must be from the appropriate anatomic section of codes.

Any procedure or service billed with an unlisted code must be appropriately documented in the medical record. The medical record should include an accurate description of the service provided, the associated results (as applicable), and clear and discernable medical necessity for the service. Clinical documentation must be submitted for reimbursement for virtually all unlisted codes. Payer review of the medical documentation will first determine whether the unlisted code is appropriate for the service provided. If there are no other applicable codes available, the payer will next review the medical record for medical necessity and appropriateness of the service.

Appropriateness of the service for new services will include analysis of safety (FDA approval, if appropriate) and efficacy of the service. You may be required to provide supplemental information that supports the safety and efficacy of the service in the form of peer-reviewed documents for some unlisted services.

Because there is no set description for these miscellaneous or unlisted procedure codes, you will need to enter a description of the service or procedure provided. Most practice management systems will provide an appropriate field to enter the description for the service provided. If you are billing the same service for more than 1 patient encounter, it is important to provide a consistent description with the unlisted procedure code.

You may also enter additional supporting information for the service, such as comparative service code(s) or code(s) that have a CPT definition and assigned reimbursement to help the payer determine both the effort and equipment required and to help determine reimbursement. Again, most practice management systems will have a field for entering this type of information. The field information, when printed on a Centers for Medicare & Medicaid Services (CMS) claim form, will display in Box 19. Note that printed documents and field length in an electronic claim are limited; be judicious in your wording. We have noted that some systems will combine fields from the description and additional information fields on the printed CMS form. As most are now billing electronically, you may not see the final format in the electronic form.

If you are entering information in all the required fields and you are still having problems with the payer processing the claim at the point of submission, you may wish to review with your practice management system vendor what limitations the system presents and how the information is parsed on the electronic claim. You may also need to speak with your payer regarding special requirements for that payer.

Any procedure or service billed with an unlisted code must be appropriately documented in the medical record. The medical record should include an accurate description of the service provided, the associated results (as applicable), and clear and discernable medical necessity for the service.

As mentioned previously, documentation of the service is often required prior to payment. Although some payers will allow submission of clinical documentation prior to initial payment review, the attachment of clinical documents to a claim is dependent on your system, clearinghouse abilities, and the payer. It may require some trial and error to determine when and how documentation can be provided to support the services provided.

Coverage of unlisted codes is a separate issue. As some unlisted codes are used to report techniques, new devices used, or new services, the payer may or may not consider the service as experimental or not covered. You should always check with your payer to determine whether the service will be covered, if possible. We understand this process is oftentimes consuming and, in many cases, will result in noncommittal or even a lack of true direction. The contact of the payer prior to provision of the service is wise.
CODING Q&A

Although these types of services require additional work, the limitations of the CPT system and the speed of code development require that a good billing department understand how to submit and follow unlisted services for adequate payment. This may also require appeal of payment amount and submission of additional supporting data such as invoices or comparative time and work estimates—be prepared and tenacious.

Q. My provider performed urodynamics for a man with benign prostatic hyperplasia (BPH) and performed a complex cystogram using calibrated electronic equipment with a pressure flow test. My provider pulled CPT codes 51728 and 51741. I didn’t see a separate uroflow test documented to bill CPT code 51741, but my provider advised me that the uroflow was recorded during the pressure flow part of the examination, so their coding was correct. Who is correct?

A. There are a number of urodynamic tests that can be performed. Urodynamic studies are not a one-size-fits-all procedure, but rather the tests performed should be chosen based upon the patient presentation and the question that needs to be answered by the urodynamic studies. Only the medically necessary tests should be billed, and only the tests that need to be performed should be performed. In this particular case, the patient had BPH-type symptoms and therefore the question that needs to be answered is whether the patient’s voiding symptoms were due to obstruction or not. This is best answered using a pressure-flow test. Therefore, the best test to perform is CPT code 51728 (Complex cystometrogram; with voiding pressure studies[ie, bladder voiding pressure]), any technique). (In addition, the add-on CPT code +51797 [Voiding pressure studies, intra-abdominal] [ie, rectal, gastric, intraperitoneal], which is an add-on code to bill with 51728 or 51729, can be billed if performed.)

The other diagnostic test that is often used for men with BPH symptoms is CPT 51741 (Complex uroflowmetry [eg, calibrated electronic equipment]). Uroflowmetry measures the urine flow electronically, with the flow rate reflecting the combined activity of the detrusor muscle, bladder neck, and urethral function. A limitation of uroflowmetry is that a decreased flow rate is not specific for obstruction or poor bladder functioning. The only way of truly differentiating obstruction from poor detrusor contraction is by a pressure flow test. If a uroflow test had previously been performed on the patient, there would be no medical necessity to perform the test again. If a pressure-flow test is being performed, there would need to be justification of medical necessity to perform a concomitant uroflow test. A pressure-flow test (CPT 51728) is a separate test from uroflowmetry, so uroflowmetry should only be billed if performed separately on separate equipment.

There are those who mistakenly believe that CPT 51741 is part of the pressure-flow tests so is always billed in addition to CPT 51728 even if there is no separate uroflow test; that is not correct. Based upon the documentation of the case listed above, we agree with you that CPT 51728 should be reported and CPT 51741 should not. Even if CPT 51741 was performed separately, we would want to see justification of medical necessity.

Q. I heard there is a new luteinizing hormone-releasing hormone (LHRH) agonist on the market that can be used for men with advanced prostate cancer called Camcevi. Is this the same as the other LHRH agonists; however, Leuprolide is FDA approved in May 2021 and is commercially available. Its main component is leuprolide, which is the same component as some of the other available LHRH agonists; however, Camcevi is leuprolide mesylate instead of leuprolide acetate. Leuprolide acetate comes in different formulations, including 1-month, 3-month, 4-month, and 6-month (7.5 mg, 22.5 mg, 30 mg, and 45 mg, respectively) preparations, whereas leuprolide mesylate is only available in a 6-month (42 mg) formulation. Camcevi comes premixed and is administered subcutaneously.

Similar to other LHRH agonists, the CPT code for administration of leuprolide is 96402 (chemotherapy administration, subcutaneous or intramuscular; hormonal antineoplastic). However, the HCPCS J-code for leuprolide acetate is J9218 (leuprolide acetate, 1 mg), whereas leuprolide mesylate is J1952 (leuprolide injectable, Camcevi, 1 mg).

Leuprolide (Camcevi) was FDA approved in May 2021 and is commercially available. Its main component is leuprolide, which is the same component as some of the other available LHRH agonists; however, Camcevi is leuprolide mesylate instead of leuprolide acetate. Leuprolide acetate comes in different formulations, including 1-month, 3-month, 4-month, and 6-month (7.5 mg, 22.5 mg, 30 mg, and 45 mg, respectively) preparations, whereas leuprolide mesylate is only available in a 6-month (42 mg) formulation. Camcevi comes premixed and is administered subcutaneously.

Send coding and reimbursement questions to Jonathan Rubenstein, MD, and Mark Painter c/o Urology Times®, at UTEditors@mjlifesciences.com.

Questions of general interest will be chosen for publication. The information in this column is designed to be authoritative, and every effort has been made to ensure its accuracy at the time it was written. However, readers are encouraged to check with their individual carrier or private payers for updates and to confirm that this information conforms to their specific rules.

UrologyTimes.com
Understanding your prescribing habits: OAB drugs

Overactive bladder (OAB) is a chronic condition that may affect up to 43% of women and a quarter of men in the US. These patients comprise a significant fraction of the typical urology practice and are candidates for several different treatments. Clinical guidelines call for the use of behavioral therapies as a first-line treatment and pharmaceutical agents as second-line therapy. In practice, then, almost all urologists prescribe medications for OAB.

Patient adherence and persistence with the medical management of OAB is a known problem that is generally attributed to lack of effectiveness, unmet expectations, or adverse effects. The association between pharmaceutical industry payments and OAB drug prescribing is less well understood. The Centers for Medicare & Medicaid Services recently updated their information on prescription claims for Medicare beneficiaries enrolled in Part D (prescription drug coverage) to include 2019 data on providers and drugs. Approximately two-thirds of Medicare beneficiaries are enrolled in Part D drug plans, and this data set is a good representation of the prescribing habits of all Medicare providers. In this article, I will review how the data reveal patterns in utilization and cost of the drugs for OAB in the Medicare population, as well as how you might interpret that information for your own use.

Drugs used to treat OAB constitute a significant number of prescriptions for the elderly. More than 13 million prescriptions of 8 generic (17 brand) drugs cost the Medicare Part D program over $1.8 billion in 2019 (approximately 1.3% of total Part D cost). Urologists prescribed more OAB drugs to Medicare beneficiaries in 2019 than any other single specialty (28%)—although, collectively, primary care physicians prescribed the most (Table 1). Urologists prescribed more expensive drugs than any other specialists and were responsible via prescribing for 37% of the total cost of OAB drugs in 2019.

Two generic drug formulations comprised more than 80% of all OAB Medicare Part D drug prescriptions in 2019: oxybutynin chloride (58%) and mirabegron (Myrbetriq; 25%). Urologists were 1.5 times more likely to prescribe mirabegron to their Medicare patients than nonurologists. It may surprise some to learn that the total retail cost of a 30-day prescription

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Providers</th>
<th>30-day fills</th>
<th>Cost</th>
<th>Specialty share cost</th>
<th>Specialty share fills</th>
<th>Cost/30-day fill</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>130,311</td>
<td>13,438,234</td>
<td>$1,836,511,094</td>
<td>100.00%</td>
<td>100.00%</td>
<td>$136.66</td>
</tr>
<tr>
<td>Urology</td>
<td>8691</td>
<td>3,709,382</td>
<td>$676,531,817</td>
<td>36.80%</td>
<td>27.60%</td>
<td>$182.38</td>
</tr>
<tr>
<td>Family practice</td>
<td>42,746</td>
<td>3,376,498</td>
<td>$337,686,599</td>
<td>18.40%</td>
<td>25.10%</td>
<td>$100.01</td>
</tr>
<tr>
<td>Internal medicine</td>
<td>34,809</td>
<td>3,147,869</td>
<td>$358,020,619</td>
<td>19.50%</td>
<td>23.40%</td>
<td>$113.73</td>
</tr>
<tr>
<td>Nurse practitioner</td>
<td>20,196</td>
<td>1,317,069</td>
<td>$180,335,203</td>
<td>9.80%</td>
<td>9.80%</td>
<td>$136.92</td>
</tr>
<tr>
<td>Physician assistant</td>
<td>8139</td>
<td>738,337</td>
<td>$113,670,059</td>
<td>6.20%</td>
<td>5.50%</td>
<td>$153.95</td>
</tr>
<tr>
<td>Obstetrics &amp; gynecology</td>
<td>5264</td>
<td>519,154</td>
<td>$99,958,895</td>
<td>5.40%</td>
<td>3.90%</td>
<td>$192.54</td>
</tr>
<tr>
<td>General practice</td>
<td>2407</td>
<td>178,520</td>
<td>$16,443,403</td>
<td>0.90%</td>
<td>1.30%</td>
<td>$92.11</td>
</tr>
<tr>
<td>Geriatric medicine</td>
<td>976</td>
<td>99,088</td>
<td>$13,555,480</td>
<td>0.70%</td>
<td>0.70%</td>
<td>$136.80</td>
</tr>
<tr>
<td>Neurology</td>
<td>1080</td>
<td>51,692</td>
<td>$6,137,886</td>
<td>0.30%</td>
<td>0.40%</td>
<td>$118.74</td>
</tr>
<tr>
<td>Others</td>
<td>6003</td>
<td>300,626</td>
<td>$34,171,134</td>
<td>1.90%</td>
<td>2.20%</td>
<td>$113.67</td>
</tr>
</tbody>
</table>

Adapted from 2019 Centers for Medicare & Medicaid Services data by Robert A. Dowling, MD

Dr. Dowling is the president of Dowling Medical Director Services, a private health care consulting firm specializing in quality improvement, clinical informatics, and health care policy affecting specialty care. He is the former medical director of a large, metropolitan, single-specialty urology group in Fort Worth, Texas.
for mirabegron ($384) is 15 times more expensive than for oxybutynin chloride ($25; Table 2). Although plan benefits are somewhat complicated and change frequently from year to year, beneficiaries typically pay approximately 25% of the drug cost during the initial coverage phase. Notwithstanding that these are 2 very different drugs with different benefit and safety profiles, the patient may see 2 drugs for the same problem but very different impacts on their wallet. Indeed, this may contribute to persistence and adherence. The cost/30-day prescription for all OAB drugs prescribed is higher than 75% of your urology peers. Keep in mind that although Medicare beneficiaries typically comprise a significant fraction of a urology practice, your prescribing habits reflected here may not be generalizable to all patients, especially commercial or Medicare Advantage plans with formulary considerations and/or step therapy requirements.

**THE BOTTOM LINE AND WHY IT MATTERS**

The 2019 Medicare data suggest urologists prescribe OAB drugs to Part D beneficiaries in higher quantities than most other specialists and tend to use more types of drugs and more expensive drugs (mirabegron) than nonurology specialties. As OAB experts, adherents of clinical guidelines, stewards of responsible prescribing, and potential recipients of industry payments, urologists should be aware of how their prescribing habits compare with urology peers and the ABU’s Lifelong Learning Program.

**REFERENCES**


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**TABLE 2. OAB DRUG METRICS BY GENERIC DRUG: UROLOGY PRESCRIBERS**

<table>
<thead>
<tr>
<th>Drug (generic)</th>
<th>Providers</th>
<th>Patients</th>
<th>30-day fills</th>
<th>% of all fills</th>
<th>Cost</th>
<th>Cost/fill</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxybutynin chloride</td>
<td>7960</td>
<td>297,705</td>
<td>1,669,180</td>
<td>45.00%</td>
<td>$41,696,745</td>
<td>$24.98</td>
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<tr>
<td>Mirabegron</td>
<td>7465</td>
<td>201,994</td>
<td>1,231,729</td>
<td>33.20%</td>
<td>$473,423,649</td>
<td>$384.36</td>
</tr>
<tr>
<td>Solifenacin succinate</td>
<td>4270</td>
<td>35,382</td>
<td>304,241</td>
<td>8.20%</td>
<td>$82,381,647</td>
<td>$270.78</td>
</tr>
<tr>
<td>Tolterodine tartrate</td>
<td>3072</td>
<td>19,822</td>
<td>185,946</td>
<td>5.00%</td>
<td>$18,106,744</td>
<td>$97.38</td>
</tr>
<tr>
<td>Trosplium chloride</td>
<td>2124</td>
<td>21,356</td>
<td>162,168</td>
<td>4.40%</td>
<td>$10,881,395</td>
<td>$67.10</td>
</tr>
<tr>
<td>Fesoterodine fumarate</td>
<td>3078</td>
<td>11,520</td>
<td>145,383</td>
<td>3.90%</td>
<td>$48,066,264</td>
<td>$330.62</td>
</tr>
<tr>
<td>Darifenacin hydrobromide</td>
<td>359</td>
<td>504</td>
<td>10,491</td>
<td>0.30%</td>
<td>$1,793,879</td>
<td>$171.00</td>
</tr>
</tbody>
</table>

**TABLE 3. NUMBER OF UNIQUE OAB DRUGS PRESCRIBED BY SPECIALTY**

<table>
<thead>
<tr>
<th>Unique OAB drugs prescribed</th>
<th>% of nonurologists</th>
<th>% of urologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60.20%</td>
<td>13.70%</td>
</tr>
<tr>
<td>2</td>
<td>25.40%</td>
<td>20.80%</td>
</tr>
<tr>
<td>3</td>
<td>9.60%</td>
<td>23.00%</td>
</tr>
<tr>
<td>4</td>
<td>3.40%</td>
<td>19.80%</td>
</tr>
<tr>
<td>5</td>
<td>1.10%</td>
<td>14.50%</td>
</tr>
<tr>
<td>6</td>
<td>0.30%</td>
<td>6.90%</td>
</tr>
<tr>
<td>7</td>
<td>0.00%</td>
<td>1.20%</td>
</tr>
</tbody>
</table>

**TABLE 4. MIRABEGRON AS A PERCENTAGE OF ALL OAB PRESCRIPTIONS UROLOGY: RANKING**

<table>
<thead>
<tr>
<th>Percentile of urologists</th>
<th>% mirabegron of all OAB prescriptions</th>
</tr>
</thead>
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OAB, overactive bladder. Adapted from 2019 Centers for Medicare & Medicaid Services data by Robert A. Dowling, MD.
What you must do to survive down markets

Being patient and showing discipline are key behaviors

The first half of 2022 has come with plenty of challenges for investors. Both domestic and international equity markets are down. As of July 11, 2022, the Dow Jones Industrial Average was down 14.70%, the S&P 500 was down 19.59%, and the MSCI EAFE was down 19.18%. Compounding these challenges is that bonds, normally a safe haven when equities are struggling, have also been down. The Bloomberg US Aggregate bond index was down 10.59%.

When markets are down significantly, investors commonly feel a sense of panic or fear they are losing everything they have accumulated. They obsess over the financial news and are tempted to sell to preserve what is left. However, these moves typically provide short-term comfort at the expense of long-term goals.

Selling after the markets are down may significantly reduce your ability to make up those losses in the rallies that historically occur after a sharp decline. For example, after the 2008-2009 financial crisis—in which the S&P 500 was down as much as 51%—the following rally lasted 118 months and was up over 300%. Following the dot-com crash in 2000, when stocks were down 45%, the following rally lasted 61 months and was up over 100%. In fact, following every sustained down market has been a significant and sustained upward rally.1

Benefiting from these rallies requires being invested in the market. If you sold previously, you may miss out on all or a significant portion of the rally. You may be thinking, “But what if I sold when things started going down, then bought back in at the bottom?” Timing the market is incredibly difficult to do. How will you know when the market is headed for a sustained downward slide? How will you know when the market has reached bottom? These are nearly impossible things to predict, and guessing wrong can negatively impact your investment success.

Surviving a down market requires some key behaviors: patience and discipline. You must have patience that markets will turn and move in an overall positive direction over the long term. This also means not chasing the hottest trends and trusting your investment strategy will produce the long-term results you desire. Discipline means continuing to adhere to an asset allocation strategy and diversified investment mix that can help you reach your financial goals. If you feel like you must take some sort of action, the following includes a few activities that can be helpful:

**Rebalance your portfolio.** Market volatility can skew your allocation from its original target. Certain assets will be more affected by market swings and will move outside their target allocations. Rebalance your portfolio by selling positions that have become overweight in relation to the rest of your portfolio and move the proceeds to positions that have become underweighted.

**Tax-loss harvesting.** In taxable accounts, if any investments are in the negative, you can sell those investments to capture the loss. These losses can be used to offset gains elsewhere, or up to $3000 per year can be used to offset income taxes. Tax-loss harvesting can help these accounts become more tax efficient moving forward.

**Review your risk tolerance.** Risk you took on years ago may no longer make sense, given your current circumstances and life stage. If you are less open to risk, consider adjusting your target asset allocation.

**Implement defensive tactics.** If you must trade during volatile markets, there are defensive steps you can take to protect your positions. Stop orders and stop-limit orders can help shield unrealized gains or limit potential losses on an existing position.

When markets are struggling, you may be tempted to take action. However, reacting during these time periods may cause more harm than good to your investment portfolios. If you must take action, consider less substantial maneuvers such as tax-loss harvesting, rebalancing, and implementing defensive tactics like stop-limit and stop-loss orders. Before taking any action, we recommend you speak with your financial professional or certified public accountant to better understand their financial or tax implications.

**REFERENCE**
Night shift work reduces physicians’ empathy for pain

JEFFREY BENDIX
Bendix is a senior editor for Medical Economics.

Working the night shift appears to make doctors less sympathetic to patients’ pain. That conclusion emerges from a newly published study of patterns of pain medication prescribing among American and Israeli emergency department (ED) doctors. It found that doctors prescribed less pain medication during night shifts than during the day. The findings were published in The Proceedings of the National Academy of Sciences.

The study consisted of 2 parts. In the first part, 67 ED physicians performed empathy assessment tasks and responded to simulated patient scenarios in the morning. The physicians either had just finished a 26-hour shift or were about to start their workday. The doctors who had recently finished a night shift consistently scored their patients low on pain assessment charts and showed decreased emotional response to pictures of people in pain.

In the second part, the authors analyzed more than 13,000 discharge letters from American and Israeli ED doctors for patients who came to the hospital in the period 2013-2020 with a chief complaint of pain, such as headache or back pain. They found that across all data sets, physicians were 20% to 30% less likely to prescribe an analgesic during nightshifts compared with daytime shifts, and prescribed fewer painkillers than were generally recommended by the World Health Organization.

The bias remained significant even after adjusting for patients’ reported level of pain, patient and physician’s demographics, type of complaint, and ED characteristics.

“Our takeaway is that night shift work is an important and previously unrecognized source of bias in pain management, likely stemming from impaired perception of pain,” Anat Perry, PhD, senior lecturer in the psychology department at Hebrew University of Jerusalem, Israel, said in an accompanying news release. “Even medical experts, who strive to provide the best care for their patients, are susceptible to the effects of a nightshift,” Perry added.

The authors suggest addressing the problem by implementing more structured pain management guidelines in hospitals and changing physicians’ work schedules.

REFERENCES

Inside the Practice™:
Treating complex BPH cases

In this video, Nicole L. Miller, MD, FACS, describes her clinical practice treating patients with complex benign prostatic hyperplasia. Miller is a professor of urology and fellowship director, Endourology and Laparoscopic Surgery, at Vanderbilt University Medical Center in Nashville, Tennessee.

To watch the video, scan the QR code or visit https://bit.ly/3RhoQdu
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Inquiries may be directed to: Mark Plante, MD, FRCS(C), FACS, Division Chief, via Kristin Allard at Kristin.Allard@uvmhealth.org.
Malpractice Consult

Patient alleged physician removed wrong testicle during surgery

Expert states less invasive options should have been considered

On May 23, 2013, a 54-year-old man presented to a urologist with pain in his right testicle. An ultrasound showed damage to the testicle, including scarring and atrophy. Approximately 15 years earlier, the patient had been accidentally kicked in the testicle by his daughter, who has cerebral palsy.

The urologist determined the patient would benefit from having the right testicle removed, as well as having the right spermatic cord and left vas deferens removed (resulting in a vasectomy of the left testicle). However, during the June 11 procedure, the urologist improperly removed the left testicle and performed a vasectomy on the right testicle.

The following day, the urologist informed the patient that the wrong testicle may have been removed. An ultrasound was later performed and confirmed the right testicle remained. The patient did not return to the urologist, but instead consulted with his primary care physician. After his swelling diminished, his pain and discomfort returned to his right testicle.

The patient-plaintiff filed suit against the urologist and his employer hospital, alleging the urologist performed the surgery when it was not proper for him to do so and performed the surgery in a negligent and reckless manner, amounting to medical malpractice. The plaintiff alleged that he was fearful that he would have to undergo another surgery and removal of his right testicle, and that he would require hormone therapy for the remainder of his life. He further alleged that the surgery caused him embarrassment, anxiety, and depression, for which he required 6 months’ counseling.

During a 3-day jury trial, the plaintiff’s expert in urology testified that the urologist failed to offer alternative treatments before proceeding with the drastic option of removing the testicle. Oral medication, spermatic cord injections, and microsurgery were all less invasive options the urologist should have considered and pursued before the orchietomy, the expert stated.

According to an operating room nurse, she had returned to the operating room during the surgery when she looked at the pathology report, which noted that the specimen removed was the left testicle. She then looked at the consent form, which noted a right orchietomy. To reconcile the discrepancy, she approached the urologist, who confirmed the contents of the pathology report and consent form. He then backed away from the operating table and sat down on the floor for a period, according to the nurse. He eventually got up, put on new gloves, resterilized himself, and completed the surgery.

The plaintiff’s counsel cited the urologist’s postoperative report, which stated, “At this point, it appeared the left testicle and cord may have been removed instead of the right one.” The plaintiff’s expert in urology testified that the urologist removed the wrong testicle because he failed to track or palpate the right spermatic cord up into the body, which the urologist admitted he failed to do. The right spermatic cord exits the external ring and is approximately 1 in to the right of the penis. If the physician tracks the cord, he will know whether he is on the left or right side. The expert concluded that the urologist was reckless when he assumed he cut the right spermatic cord without confirmation.

In defense, the urologist testified that he noticed there was a problem when he attempted to perform the left vasectomy and the left testicle was missing. He maintained that he believed he removed the right testicle, as he removed the testicle that was on the right side of the scrotum. He testified that the testicle had a spermatic cord that led to the left side of the body. On cross-examination, the urologist conceded that if he, in fact, removed the left testicle when the right testicle was planned for removal, that he breached the standard of care.

The plaintiff’s expert in urology refuted the urologist’s explanation that the left spermatic cord crossed with the right. According to the expert, that is anatomically impossible, as the scrotal septum prevents the testicles from moving to different sides, in addition to the fact that the spermatic cords are not long enough to allow such an occurrence.

The hospital admitted the urologist had been an agent of the hospital at the time of the surgery, and it was responsible for any negligence committed. After a 3-day trial, the jury deliberated 80 minutes before rendering a plaintiff’s verdict, finding that the urologist breached the standard of care and proximately caused the plaintiff injury. The jurors awarded the plaintiff $870,000.

LEGAL PERSPECTIVE

Although the urologist’s testimony that he thought he was removing the right testicle may have been believable to some jurors, conceding that he breached the standard of care in removing the wrong testicle likely sealed his fate.
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