Few physicians will argue that prior authorization is an administrative headache. Now, however, there are mounting data showing that prior authorization does more harm than good. But experts say there have been few meaningful changes in processes required to obtain payer authorization to prescribe certain drugs, order tests, or perform treatments.

“As urologists we’re hit in all areas with prior authorization,” said William C. Reha, MD, MBA, a urologist in Woodbridge, VA who is the American Association of Clinical Urologists (AACU) State Advocacy Network chair and an AMA delegate to the Medical Society of Virginia.

The morning of his interview with Urology Times, Dr. Reha said members of his staff were “pulling their hair out” trying to get approval for an MRI in a man with an elevated PSA to rule out prostate cancer.

Christopher Bayne, MD, a pediatric urologist at the University of Florida, Gainesville, took to Twitter when insurer Sunshine Health denied coverage for his 13-year-old patient’s hypospadias repair.

Dr. Bayne said his own documentation may have resulted in the denial, when he wrote that the repair wasn’t medically necessary. But Dr. Bayne, who has spent time trying to convince Sunshine Health that having a normal-looking penis is necessary for the boy’s psychological well-being, said his words fell on deaf ears.

“I think it’s important to understand that teenagers are very cognizant of their genitalia and sexual maturation. Suddenly, this boy who is very shy and timid is told that his penis is abnormal. I think it’s going to have pretty dramatic consequences potentially,” Dr. Bayne said.

Dr. Bayne compares covering hypospadias repair more than an administrative hassle, it harms patients, research shows

What the future holds in trauma/reconstruction

In this interview, Richard Santucci, MD, of Crane Surgical Services in Austin, TX, discusses current trends in urologic trauma/reconstruction as well as the promise of penile transplantation.

Please see PRIOR AUTH, on page 34


IMPACT OF PRIOR AUTHORIZATION

| **Urology practices spend 14 hours per week on average on prior authorization**¹ | **A urology practice’s average preauthorization call takes 19-20 minutes** | **90% of urologists report preauthorization delays access to care and harms patient care**¹ | **28% of physicians say prior authorization has led to a serious adverse event**² | **Cost to practices of interactions with plans is $23-$31 billion annually**³ |

For the full article, please turn to page 32
When treating challenging conditions in urology, urologists often face a tough choice: take their chances with organ-sparing approaches or opt for radical surgery and potentially expose the patient to complications or sequelae.

Too often, there’s no right tool for the job.

That’s why UroGen Pharma has developed a novel technology platform designed to facilitate intracavitary treatment of challenging urological conditions.

**Introducing RTGel**

RTGel is a sustained-release hydrogel formulation that is liquid at lower temperatures and converts to gel form at body temperature. Administered via local instillation under chilled conditions, RTGel enters the target organ as a liquid, filling and conforming to the specific anatomy. After conversion to gel form, RTGel gradually releases active drug over a period of several hours before being excreted.

**Therapeutic potential**

RTGel increases dwell time and exposure of active drugs, potentially improving the therapeutic effects of urological therapies.

**It has the potential to increase the viability of organ-sparing techniques and give urologists a novel alternative to radical surgery.**

RTGel is compatible with a number of active drug products. The technology is currently being investigated in drug formulations for the treatment of low-grade upper tract urothelial carcinoma (UTUC), low-grade non-muscle-invasive bladder cancer (NMIBC), and overactive bladder (OAB).

To learn more about RTGel, visit urogen.com/innovation

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**About UroGen**

UroGen Pharma is a clinical-stage biopharmaceutical company focused on developing innovative solutions to address unmet needs in the fields of urology and uro-oncology.

**Transforming local therapies in urology**


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Post-prosthesis infection data alter conventional thinking

The research by Gross et al provides important grounds for reconceptualizing infectious complications associated with penile prosthesis surgery (see page 4). The observations that penile prosthesis surgical infections occur early are frequently associated with anaerobic bacterial organisms and that these infections overall comprise diverse pathogens including fungal organisms fundamentally alter conventional thinking related to this topic area.

Previous thinking considered primarily gram-positive bacterial organisms with antibiotic coverage directed accordingly. Prosthetic surgeons may wish to consider this new information strongly in applying revised antimicrobial protocols for penile prosthetic surgery.

Although prosthesis device infection is an infrequently occurring complication of prosthetic surgery in modern times, it is generally recognized that it represents the most serious complication risk of this surgery. Device loss (removal) and penile tissue damage are common sequelae of this complication. It is acknowledged that in the acute setting, salvage approaches such as the Mulcahy procedure have been used successfully under select indications.

In accordance with clinical guidelines, surgeons are advised to inform patients about the potential risk of device infection associated with this procedure. To mitigate this risk, good practice is to administer antibiotics perioperatively despite the rigor of deferring surgery in the presence of active clinical infection and performing the surgery with meticulous technique.

No consensus position exists as to the established antimicrobial regimen to be used for penile prosthetic surgery. Antibiotic regimens generally feature a gram-positive-directing antimicrobial agent such as vancomycin or a cephalosporin, in combination with a gram-negative-directing antimicrobial agent such as an aminoglycoside. Expanded coverage to include agents directed toward anaerobic and fungal organisms warrants consideration given today’s paradigm shift.

It is accepted that this report may not represent a definitive organism profile registry, although the large multi-institutional effort here is commendable. It is acknowledged as well that only a rigorous comparative study of antimicrobial agents and regimens may affirm the optimal infectious disease approach. However, such a future study is unlikely to be provocative given the low frequency of prosthetic device infection. Ongoing science of prosthetic infections including biofilm microbiology may also be advantageous to advance strategies to counteract infection risk.
SAN FRANCISCO—Isolated anaerobic organisms appear to occur most rapidly on average when infections occur following surgical intervention with an inflatable penile prosthesis (IPP), according to data presented at the 2018 AUA annual meeting in San Francisco.

Researchers found that gram-negative organisms have the longest delay between device implantation and surgical management of infection.

The authors examined the timeline of microorganisms, infection severity, and surgical intervention in men who received an IPP. They found that 71% of anaerobic infections underwent successful salvage compared with 64% of gram-positive infections. Successful salvage rates were 60% in men with fungal infections and 59% in men with gram-negative infections.

“Have you to be vigilant throughout the first year after penile prosthesis placement, and there seem to be particular trends as far as what is presenting when,” said first author Martin Gross, MD, clinical assistant professor of surgery at Dartmouth College’s Geisel School of Medicine, Hanover, NH.

Dr. Gross and his co-authors reviewed a multi-institution database of IPP infections to look for patterns regarding organisms discovered at salvage or explant surgery. They also examined interventions deemed necessary by contributing surgeons based on severity of infection. This retrospective analysis included 221 patients at 26 institutions who underwent salvage procedure or device explant between 2001 and 2016.

Seven isolated anaerobic infections were treated an average of 2.6 months after device implantation (range, 1 to 7.5 months), the study showed. In addition, clinicians treated 62 isolated gram-positive infections an average of 4.5 months after device implantation (range, 2 weeks to 27 months) and 14 isolated fungal infections an average of 5.8 months after device implantation (range, 2 weeks to 58 months).

The authors found that among the seven anaerobic infections, five devices underwent successful malleable implant salvage (71%) and the other two were explanted.

How gram-positive infections were treated

Dr. Gross, who presented the study findings at the meeting, said that among the 62 gram-positive infections, 25 devices underwent successful malleable implant salvage (40%), 22 were explanted (35%), and 15 underwent classic Mulcahy salvage (24%). Among the 14 fungal infections, four patients had malleable implant salvage (40%), four devices were explanted (40%), and four were salvaged using the classic Mulcahy technique (20%). Among the 39 gram-negative infections, the findings were similar, with 10 undergoing malleable implant salvage (26%), 16 devices explanted (41%), and 13 salvaged in the classic Mulcahy technique (33%).

“What we are seeing is very different from what the AUA guidelines are designed to protect against. The AUA guidelines were designed for the bacteria we were seeing 20 to 25 years ago,” said Dr. Gross. “We are now getting bacteria that are different. The AUA guidelines need to be updated.”

Dr. Gross is a consultant for Coloplast.

### Table: Incidence, Timing of Post-IPP Infections

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Number of Infections</th>
<th>Average Time of Treatment Following Device Implantation (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated anaerobic infections</td>
<td>7</td>
<td>2.6</td>
</tr>
<tr>
<td>Isolated gram-positive infections</td>
<td>62</td>
<td>4.5</td>
</tr>
<tr>
<td>Isolated fungal infections</td>
<td>14</td>
<td>5.8</td>
</tr>
<tr>
<td>Isolated gram-negative infections</td>
<td>39</td>
<td>6.96</td>
</tr>
</tbody>
</table>

Source: Martin Gross, MD

“Anaerobic infections are presenting first, gram-positive infections are next, and then slower infections such as fungal infections and gram-negative infections are really later on by the middle of the year. And by the end of the year, multi-organism infections are more likely to be presenting,” Dr. Gross said in an interview with Urology Times.

The study showed that 24 multi-organism infections were treated an average of 5.2 months after device implantation (range, 2 weeks to 27 months), and 67 infections had no growth seen in culture but were treated an average of 4 months after implantation (range, 2 weeks to 58 months).

In Brief

Higher Adolescent BMI Linked With Increased RCC Risk

Being overweight has been linked with renal cell carcinoma (RCC) among adults, but it’s unclear if this risk is present during adolescence.

In an International Journal of Cancer study of adolescents who were followed for 37 years, researchers observed a trend for higher RCC risk with increasing body mass index during adolescence, where one-unit increase in body mass index conferred a 6% increased risk of RCC (Int J Cancer Feb. 20, 2019 [Epub ahead of print]).

The study included 238,788 Swedish men who underwent mandatory military conscription assessment between 1969 and 1976 at an average age of 18.5 years. Over the next 37 years, 266 men were diagnosed with RCC.

“New data supporting a link between adolescent overweight/obesity—alone and in combination with low physical working capacity—and renal cancer adds further important evidence supporting the implementation of early interventions within the rapidly growing group of overweight and obese teenagers,” said co-author Pernilla Sundqvist, MD, PhD, of University Hospital Örebro, in Sweden.
**Tissue sealing sheets may improve post-RP function**

Erectile function recovery rates better in fibrin-treated patients vs. controls

**John Schieszer**
UT Correspondent

**SAN FRANCISCO—**Erectile function after robot-assisted laparoscopic prostatectomy (RARP) may be better in patients who are treated with fibrin tissue sealing sheets, according to interim results from a randomized controlled trial conducted in Japan.

Investigators reported at the 2018 AUA annual meeting in San Francisco that definitive data with longer follow-up periods are needed to confirm the findings, but they may suggest a useful therapeutic approach to improve erectile dysfunction (ED) after nerve-sparing RARP.

“In the patients who had bilateral nerve-sparing surgery, the recovery rates of erectile function at 12 months after radical prostatectomy were 52% in the sheet group and 40% in the control group,” said lead study investigator Shinichi Yamashita, MD, who is with the Tohoku University Graduate School of Medicine in Sendai.

Recovery rates for ED following RP remain unsatisfactory, he said, even with nerve-sparing RARP. Recently in Japan, a tissue sealing sheet (TachoSil) has been used to prevent intraoperative bleeding in RP. The product is a collagen sponge that is coated on one side with human coagulation factors fibrinogen and thrombin. Upon contact with blood or other fluids, the coagulation factors react to form a fibrin clot and prevent re-bleeding or effusion, said Dr. Yamashita, who presented the study findings at the meeting.

In the U.S., TachoSil is currently indicated “for use with manual compression in adult and pediatric patients as an adjunct to hemostasis in cardiovascular and hepatic surgery, when control of bleeding by standard surgical techniques (such as suture, ligature or cautery) is ineffective or impractical,” according to manufacturer Baxter Healthcare Corp.

Dr. Yamashita said the team previously found that the tissue sealing sheet attenuated postoperative inflammatory changes and improved erectile function following cavernous nerve dissection in a rat model of nerve-sparing RP.

In the current investigation, the authors examined the efficacy of tissue sealing sheets for erectile function after nerve-sparing RARP in a large group of men. A total of 142 patients with prostate cancer were randomized between January 2014 and March 2017 for nerve-sparing RARP with or without the tissue sealing sheets.

In this study, men with severe ED were excluded. In the treatment arm, the spared neurovascular bundles were covered with the tissue sealing sheets immediately after removal of the prostate. The authors evaluated erectile function prospectively and at 1-, 3-, 6-, and 12-month periods after RARP using the Expanded Prostate Cancer Index Composite questionnaire.

Dr. Yamashita said 72 men (median age, 65 years) underwent RARP with the tissue sealing sheets. There were 46 men (64%) who had bilateral and 26 men (36%) who had unilateral nerve-sparing procedures in the sheet group. In the control group, 46 men (66%) had bilateral and 24 (34%) had unilateral nerve-sparing procedures. The study demonstrated no significant differences between the groups in operating times and estimated blood loss.

In the sheet group, the recovery rate of erectile function was 14% at 1 month, 20% at 3 months, 31% at 6 months, and 47% at 12 months. That compared to 24% (1 month), 28% (3 months), 31% (6 months), and 36% (12 months) in the control group.

“The recovery rates of erectile function after RARP in the patients with the tissue sealing sheets were better than those without the sheets,” Dr. Yamashita said. “Definitive data with longer follow-up periods are needed to confirm the tissue sealant sheet affects erectile function over time.”

**View findings as exploratory**

John P. Mulhall, MD, director of the male sexual and reproductive medicine program at Memorial Sloan Kettering Medical Center, New York, said there were six surgeons in this current series and that is something that has to be considered. He said these findings must be viewed as exploratory.

“The other concerns are that they used a fairly unique scoring system for recovery. They were looking at percentage from baseline score. What they didn’t present and what they need to present in their paper would be the minimally clinically important difference in that score,” Dr. Mulhall told *Urology Times*. “They are to be congratulated because it is a randomized trial, which is very difficult to do. We look forward to seeing 24-month data.”

**“They are to be congratulated because it is a randomized trial, which is very difficult to do. We look forward to seeing 24-month data.”**

**JOHN P. MULHALL, MD**

Ahmad Majzoub, MD, who attended the presentation, said more research is needed but he expects the product to be widely adopted.

“I believe it is a very sound procedure and a sound technique to do. Using some sort of method or technique to preserve the function of these nerves would definitely help improve outcomes,” said Dr. Majzoub, associate consultant in urology at Hamad Medical Corp., Doha, Qatar.

The study was supported by Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Science. UT

**TABLE**

<table>
<thead>
<tr>
<th>TISSUE SEALING SHEETS’ EFFECT ON POST-RARP FUNCTION</th>
<th>Tissue sealing sheet group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erectile function (EF) recovery, 1 month post-RARP</td>
<td>14%</td>
<td>24%</td>
</tr>
<tr>
<td>EF recovery, 3 months post-RARP</td>
<td>20%</td>
<td>28%</td>
</tr>
<tr>
<td>EF recovery, 6 months post-RARP</td>
<td>31%</td>
<td>31%</td>
</tr>
<tr>
<td>EF recovery, 12 months post-RARP</td>
<td>47%</td>
<td>36%</td>
</tr>
</tbody>
</table>

Source: Shinichi Yamashita, MD
Emergent setting linked to lost follow-up for stents

Cheryl Guttman Krader
UT Contributing Editor

Patients with ureteral stents are rarely lost to follow-up, but the risk is increased when patients are stented in an emergent setting rather than as part of an elective procedure, Yale University urologists reported at the 2018 World Congress of Endourology in Paris.

In order to minimize the incidence of these potentially impactful events, the authors underscored the importance of thoroughly counseling patients treated in an emergent setting about the need for follow-up care. They also advocated for the use of an electronic health record system to facilitate the identification and follow-up of patients with forgotten stents.

Using their EHR system (Epic), the authors identified 1,778 patients who had a ureteral stent placed from January 2015 to August 2017, of whom 16 (0.9%) had a stent in place for >90 days. A multivariate logistic regression analysis was performed to identify variables predicting the latter patients with a “forgotten” stent and found statistically significant associations with emergent surgery, which increased the risk by 3.5-fold, and African-American race, which predicted a 4-fold increased risk.

Demographic characteristics (sex and age) and type of insurance coverage were not independent predictors for having a long-retained stent.

“Lost ureteral stents are a low-probability event, but can affect a significant number of patients given that ureteral stent placement is a commonly performed procedure,” said first author Juan F. Javier-DesLoges, MD, a urology resident at Yale University, New Haven, CT.

“Our study supports the need to intensively counsel patients treated in an emergent setting so that they understand the need for stent removal and for providers to be proactive in scheduling a return visit. Considering that we routinely counsel patients treated in an emergent setting and that patient compliance is a variable beyond our control, there is also a need for a safety net system to identify patients lost to follow-up.”

“As a means to minimize and prevent the morbidity and mortality associated with retained stents, we encourage providers with access to the Epic EMR to use this resource to track all patients with ureteral stents,” said senior author Piruz Motamedinia, MD, associate professor of urology at Yale.

With colleagues in the urology and IT departments at their center, Dr. Motamedinia and Patrick Kenney, MD, worked to create a workflow in their EMR to log insertion and removal of ureteral stents and to identify and report patients with stents retained >90 days. The latter individuals are then contacted for retrieval.

Several benefits to using EHR

“Using an EMR-linked protocol for tracking ureteral stent patients has several benefits,” Dr. Motamedinia said. “First, it is an automated system that does not rely on prospective inputting by a provider for the sole purpose of stent tracking. In addition, no third party is involved, it is HIPAA compliant, and it includes all providers in the health care system, which allows it to be a quality initiative.”

The authors noted that although African-American race was independently associated with increased risk for a retained stent, they believe the finding was confounded by unmeasured variables.

“Black race is probably a surrogate for one or more variables we cannot account for,” said Dr. Motamedinia.

They discounted the possibility that the association with race reflected access to health care.

“We believe insurance status correlates more closely with access to health care than race, and when we look at an effect of insurance status by comparing patients who had Medicare or Medicaid coverage to those with commercial insurance, we did not find that insurance status was associated with having a forgotten stent,” Dr. Javier-DesLoges said.

“Lost ureteral stents are a low-probability event, but can affect a significant number of patients given that ureteral stent placement is a commonly performed procedure,” said first author Juan F. Javier-DesLoges, MD, a urology resident at Yale University, New Haven, CT.

“Our study supports the need to intensively counsel patients treated in an emergent setting so that they understand the need for stent removal and for providers to be proactive in scheduling a return visit.”

Juan F. Javier-DesLoges, MD

‘Y’tube Videos

Y’tube is a video resource for urologists and other physicians who focus on men’s health. Videos cover surgical aspects of a variety of men’s health issues, with the goal of providing clinicians a current reference.

James M. Hotaling, MD, MS | Section Editor  urologytimes.com/YTUBE

Michael P. Kurtz, MD, MPH, and Caleb P. Nelson, MD

Dr. Kurtz and Dr. Nelson illustrate a case of semi-rigid ureteroscopy with laser lithotripsy for ureteral stone in a child, who is rendered stone free without pre-stenting.

Pankaj P. Dangle, MD

In this video, pediatric URS is shown to be safe and feasible without long-term sequelae on the ureters.

Gregory E. Tasian, MD, MSc, MSCE (Reviewer)

Dr. Tasian provides expert commentary on the two videos submitted for this month’s installment.

Jonathan S. Ellison, MD

This video of bilateral URS in a 16-year-old male with cystinuria highlights several pragmatic strategies for efficient URS.

Urology Times | MARCH 2019

6
Device measures force during UAS insertion
Sensor could increase physician comfort with ureteral access sheath utilization

Cheryl Guttman Krader
UT Contributing Editor

A novel investigational ureteral access sheath force sensor (UAS-FS) served as an effective tool for the safe deployment of a ureteral access sheath in initial clinical experience, researchers reported at the 2018 World Congress of Endourology and SWL in Paris.

The UAS-FS was developed at the University of California, Irvine. Used in conjunction with fluoroscopy, it continuously measures force during UAS insertion, displays the data in a digital readout, and gives auditory and visual alerts when a preset maximum force is reached.

“I am a strong proponent for the use of a ureteral access sheath because I know it reduces intrarenal pressure and significantly reduces risk of sepsis. I also believe it might improve stone-free rates and therefore the number of procedures patients undergo. Concern over causing ureteral injury during UAS passage, however, has limited its uptake among urologists,” said Kamaljit Kaler, MD, clinical assistant professor at the University of Calgary, Southern Alberta Institute of Urology in Calgary.

“Our experience indicates that the UAS-FS is a useful adjunctive safety tool that could afford urologists greater comfort and confidence with UAS insertion.”

As a fellow in endourology, image-guided therapy, and robotic surgery at the University of California, Irvine, Dr. Kaler and his mentor, Ralph Clayman, MD, had the vision for developing a device that could provide live feedback on UAS deployment force in order to prevent clinically significant ureteral injury. They collaborated on the design with colleagues in the department of engineering at the University of California, Irvine. The team’s goal is to bring the UAS-FS onto the market as a disposable or reusable device.

The protocol for clinical investigation of the UAS-FS considered findings from initial testing in a porcine model that showed ureteral injury occurred during UAS insertion when the peak force reached 8 Newtons (N). In the clinical trial, UAS insertion was initiated using a 14/16F device. If the level of applied force reached 7-8 N, a fluoroscopic image was obtained, and the UAS was removed and downsized to a 12/14F sheath. If the force during its insertion reached the upper limit, the sheath was withdrawn and replaced with a 9.5/11F sheath.

Four urologists are participating in the clinical trial. Data were analyzed from 56 patients undergoing routine ureteroscopy. There were 64 UAS deployments in the series; 39 (61%) were completed at a force <8 N using a 16F UAS, 18 (28%) were done with a 14F UAS, and seven (11%) used an 11F device.

The post-ureteroscopic lesion scale (PULS) grade averaged 0.76 and was 0-2 in all patients except one. The latter case involved a PULS 3 injury in a patient who underwent serial insertion of three sheaths; peak forces reached 8.1 N initially with a 16F UAS, 8.9 N with a 14F UAS, and 5.0 N using an 11F UAS. The patient had no symptomatic or radiographic evidence of stricture when followed at 2 months.

“Based on this study and further porcine studies, Dr. Clayman has decreased the force threshold to 5-6 N in an attempt to entirely eliminate the risk of injury. In our study, no patients had a PULS score >1 when we limited the insertion force to <5 N,” Dr. Kaler said.

No difference with tamsulosin
Thirty-seven (66%) of the patients in the study received oral tamsulosin (Flomax) for up to 1 week prior to ureteroscopy. There was no significant difference in the mean initial peak pressure reached comparing patients treated with tamsulosin with the group that did not.

“Tamsulosin can help induce a state of ureteral relaxation, and we found previously in a retrospective study that the 16F UAS deployment rate was significantly higher among patients receiving preoperative tamsulosin than in those who did not,” Dr. Kaler said.

“Considering that previous endoscopic intervention could result in ureteral dilation and facilitate UAS insertion, we are now analyzing the data from our UAS-FS study to see if such a history could be a confounding factor explaining the observed lack of effect of tamsulosin pretreatment on peak pressure.”

“Anecdotally,” he added, “I have been starting all patients undergoing percutaneous nephrolithotomy or ureteroscopy on tamsulosin 1 week prior to their procedure and have not yet had a single case where I was unable to insert a UAS.”

The University of California Irvine, Dr. Clayman, and Dr. Kaler hold patents on the UAS-FS. UT

No-Scalpel Vasectomy Instruments

<table>
<thead>
<tr>
<th>Instrument Set</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>ASSI-VAS 47626</td>
<td>NO-SCALPEL VASECTOMY FORCEPS 12.5cm, 5 in.; with sharp pointed smooth curved jaw, Gold handles</td>
</tr>
<tr>
<td>ASSI-VAS 47726</td>
<td>NO-SCALPEL VASECTOMY FORCEPS 12.5cm, 5 in.; very delicate curved, smooth pointed jaw, Gold handles</td>
</tr>
<tr>
<td>ASSI-VAS 47526</td>
<td>NO-SCALPEL VASECTOMY FIXATOR RING CLAMP FORCEPS 14cm, 5.5 in.; with blunt tips, standard ring, Gold handles</td>
</tr>
<tr>
<td>ASSI-VAS 46326</td>
<td>NO-SCALPEL VASECTOMY FIXATOR RING CLAMP FORCEPS 14cm, 5.5 in.; with blunt tips, small ring, Gold handles</td>
</tr>
</tbody>
</table>

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Routine PET/CT not beneficial for node-negative patients

Andrew D. Bowser
UT Correspondent

PHOENIX—Routine use of positron emission tomography/computed tomography prior to radical cystectomy is unlikely to benefit clinically node-negative patients, results of a recent investigation suggest.

Instead, the primary role of PET/CT appears to be further evaluation of enlarged nodes identified by CT, according to the study authors, who looked at the diagnostic properties of PET/CT in more than 200 patients with muscle-invasive urothelial carcinoma.

Based on the findings, PET/CT should be used when its results would impact patient management, such as the patient with clinically positive lymph nodes that would benefit from further characterization, according to first author Shawn Dason, MD, a urologic oncology fellow at Memorial Sloan Kettering Cancer Center, New York.

“We are seeing PET/CT being increasingly performed as a routine preoperative test before radical cystectomy, but this is unlikely to benefit most patients without a suspicious CT scan,” Dr. Dason said in an interview with Urology Times.

The study, presented at the 2018 Society of Urologic Oncology annual meeting in Phoenix by co-author Nathan C. Wong, MD, also a urologic oncology fellow at Memorial Sloan Kettering Cancer Center, New York, looked at the diagnostic properties of PET/CT according to the study authors, who worked on the study with Bernard H. Bochner, MD, and colleagues.

Specifically, PET/CT rarely detected pathologically node-positive disease, with a sensitivity of 7% to 23% on a per-patient or per-region level, according to the investigators.

Ruling out positive lymph node disease

By contrast, a negative PET/CT was useful in ruling out positive lymph node disease, according to investigators, with a specificity of 92% to 100% and a specificity of 63% to 81%.

That suggests PET/CT can help eliminate uncertainty as to whether patients with small but enlarged nodes truly have actual lymph node metastases, according to the investigators.

“We are seeing PET/CT being increasingly performed as a routine preoperative test before radical cystectomy, but this is unlikely to benefit most patients without a suspicious CT scan.”

SHAWN DASON, MD

“These patients could have a biopsy, but this is invasive, and some of these lesions are difficult to biopsy,” said Dr. Dason.

These findings corroborate results of an earlier study in a more advanced setting. That study, published in 2010 by investigators at Memorial Sloan Kettering and Weill Medical College of Cornell University, suggested that a negative PET/CT result was helpful in ruling out metastatic involvement of a suspicious lesion on CT scan (J Clin Oncol 2010; 28:3973-8).

The benefit of routine preoperative PET/CT in earlier disease was unclear based on the results of earlier investigations, according to Dr. Dason. Those studies included heterogeneous patient populations and varied in terms of how they handled preoperative chemotherapy and clinically suspicious lymph nodes on a regular CT scan. UT

Minimally invasive cystectomy linked with shorter hospital stay

Andrew D. Bowser
UT Correspondent

PHOENIX—Compared to an open approach, minimally invasive radical cystectomy was associated with a near 2-day shorter hospital stay in bladder cancer patients treated at diverse institutions across the United States, according to authors of a recent retrospective analysis of Medicare claims.

There was no difference in readmission rates for minimally invasive versus open radical cystectomy, while the cost to Medicare was nearly $4,000 less for the minimally invasive procedure, according to the analysis, which was presented at the 2018 Society of Urologic Oncology annual meeting in Phoenix and published in Urology (Oct. 23, 2018 [Epub ahead of print]).

“The real-world practice of robotic cystectomy appears to line up with that in high-volume centers in randomized trials, which is reassuring for us,” said researcher Parth K. Modi, MD, MS, a urologic oncology and health services research fellow at the University of Michigan, Ann Arbor, working with Chad Ellimoottil, MD, MS, and colleagues.

Specifically, these findings confirm and extend those of the randomized RAZOR trial, Dr. Modi told Urology Times. In that phase III, non-inferiority study, which included 350 patients treated at 15 high-volume, specialized centers, median length of stay was significantly shorter for those patients who underwent robot-assisted radical cystectomy versus those who underwent an open procedure (Lancet 2018; 391:2525-36).

However, cost data in RAZOR were unsuitable for analysis, according to investigators, who cited “considerable heterogeneity” in data among centers and an inability to collect data from all participating centers due to propriety concerns.

For the analysis presented at the SUO annual meeting, Dr. Modi and colleagues looked at 4,760 Medicare patients with bladder cancer who underwent radical cystectomy between 2008 and 2015. Of those patients, 693 (14.6%) underwent a minimally invasive procedure, while the remaining 4,067 (85.4%) were open.

Length of stay was a median 10.1 days for the minimally invasive procedure versus 11.9 days for the open procedure (p<0.001) after adjusting for patient, hospital, and surgeon factors, Dr. Modi and colleagues reported. By contrast, 30-day
Germline BRCA2 status may be linked to PCa outcomes

Outcomes linked with mutation may be modified by initial Tx approach

John Schieszer / UT Correspondent

Germline BRCA2 status may be of assistance to clinicians when determining initial treatment for men with metastatic castration-resistant prostate cancer (mCRPC), according to a new study published in the *Journal of Clinical Oncology* (2019; 37:490-503).

It is well-established that germline mutations in DNA damage repair (gDDR) genes affect a significant proportion of patients with mCRPC. However, the clinical implications of this finding have remained unclear.

“This study is important because it brings us one step closer to the incorporation of these tests into clinical practice. Not only does germline screening have the potential to guide treatment selection, as in this study, but to also improve patient selection for prostate cancer screening and decisions for biopsy and treatment,” said urologic oncologist Daniel Oberlin, MD, of Golden Gate Urology in San Francisco, in an interview with Urology Times sister brand Cancer Network.

Dr. Oberlin, who was not involved with the study, also noted that huge advancements in genetic sequencing technologies over just the last 10 years have significantly improved the ability to study the genetic influencers of prostate cancer.

Elena Castro, MD, PhD, clinician scientist at the Spanish National Cancer Research Center in Madrid, and colleagues prospectively enrolled unselected patients with mCRPC and screened them for gDDR mutations in 107 genes. They then examined the impact of ATM/BRCA1/BRCA2/PALB2 germline mutations on cause-specific survival (CSS).

The association between gDDR subgroups and response outcomes for mCRPC treatments was also evaluated. As part of the investigation, the authors explored combined progression-free survival from the first systemic therapy (PFS1) until progression on the second systemic therapy (PFS2).

Of 419 eligible patients, 68 carriers were identified (16.2%); of these, 14 had mutations in BRCA2, eight had mutations in ATM, four had mutations in BRCA1, and none had PALB2 mutations. The study was not able to reach its primary endpoint because the difference in CSS between ATM/BRCA1/BRCA2/PALB2 carriers and non-carriers was not statistically significant. However, CSS was approximately 50% lower in germline BRCA2 (gBRCA2) carriers versus non-carriers (17.4 vs. 33.2 months, respectively).

Significant interactions were found between gBRCA2 status and treatment type (androgen signaling inhibitor vs taxane therapy). CSS was 24.0 months in gBRCA2 carriers treated with abiraterone (ZYTIGA) or enzalutamide (XTANDI) as first-line therapy compared with 17.0 months for those treated with taxanes. PFS2 was 18.9 months in gBRCA2 carriers treated first-line with abiraterone or enzalutamide compared with 8.6 months with taxanes. The study showed no differences in clinical outcomes by treatment type in non-carriers.

The results of this study suggest that outcomes associated with gBRCA2 may be modified by the initial treatment approach, according to the researchers. They theorized that gBRCA2 mutations have a deleterious impact on mCRPC outcomes, but may be affected by treatment type as well as by treatment sequence. However, these findings are based on only a small number of patients and require additional validation, they concluded.

**CYSTECTOMY**

*continued from page 8*

readmission rates were not significantly different, at 27.4% and 26.8% for the minimally invasive and open approach, respectively (p=.77).

**Episode spending lower for MIS**

Total Medicare payments within 90 days of surgery were significantly lower for minimally invasive versus open radical cystectomy, at $34,369 and $38,071, respectively, in adjusted multiple regression analysis (p<.001).

Dr. Modi said it was somewhat surprising that 90-day episode spending was lower for the minimally invasive approach, given a previous analysis showing the opposite—that the minimally invasive approach was associated with higher 90-day spending (*Eur Urol* 2016; 70:195-202).

That previous analysis focused on an earlier time period, 2002-2012—earlier in the adoption of minimally invasive technology—which could mean that higher spending was due to inexperience or more “cautious” postoperative management, Dr. Modi said.

Mortality outcomes of minimally invasive versus open radical cystectomy were not analyzed in the current study due to the short time frame evaluated, and oncologic outcomes were not available in the Medicare data, according to Dr. Modi.

“It’s possible that there are patient factors that we were unable to account for in our analysis, and so we wouldn’t make any strong claims about the effectiveness of robotic cystectomy based on this data,” he said. “A randomized trial really is the best way to answer those types of questions.”

Effectiveness of robotic cystectomy was the main focus of the randomized, phase III RAZOR trial. In the *Lancet* report on the study, RAZOR investigators said robot-assisted radical cystectomy was noninferior to open radical cystectomy with regard to the clinical primary endpoint of progression-free survival.

Source: Parth K. Modi, MD, MS

**FIGURE / Minimally invasive vs. open cystectomy: Length of stay**

<table>
<thead>
<tr>
<th></th>
<th>Minimally invasive procedure</th>
<th>Open procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median length of stay (days)</td>
<td>10.1</td>
<td>11.9</td>
</tr>
</tbody>
</table>

Source: Parth K. Modi, MD, MS

MARCH 2019 | Urology Times | 9
Academic success is defined by rank, number of publications, grants, leadership in professional organizations, and peer recognition. Less recognized is the string of failed trials, rejections, and—even more important—personal sacrifices to achieve that success. The net balance is often recognized too late to recoup the losses. If you are lucky, an opportunity presents midway through your career to balance the two sides orcurtail the desire to succeed at any cost. This is an account of all my professional failures, as personal ones are for only those who need to forgive. I offer it not as self-criticism but as a handful of lessons for others to learn from.

**Failure to train for academic pursuit**

The medical school training in India did not prepare me for an academic career. The training was rich in clinical learning but poor in accounting for outcomes, basic research, statistics, and writing. It came only during and after fellowship and association with Dr. Arthur Smith, who started me on my publications. Seeing my name in print was heady, and after a while it became a necessity. Only late in my career did it become a habit. Many helped me write, but what helped most were the rejections from journals that stoked my passion to succeed.

What lesson did I learn? Statistics is important, and writing skills are invaluable. Mastering the search engines and reference tools is automatic for today’s learners, but few pursue beyond Google and in-depth reading is becoming rare.

**Failure in writing grants and IRB**

It took many years before I achieved my cherished goal of receiving grant funding. Industry trials were the early successes but led me away from the serious science of grant writing. It is a skill acquired best by writing for institutional review board approvals and seeking grants as a student or resident.

Independent, peer-reviewed small grants are far more valuable than large, multicenter device grants. While I valued the opportunity to participate in all the trials, it certainly delayed the scientific pursuit. Zigzagging or changing course of research becomes the path that pursues the dollars; strict, goal-oriented scientific pursuit is a hard road with a very low chance of funding. Team science is an approach that should come early in life rather than late, as it came to me. Multiple failures to earn a good score in applying for NIH grants were based on solitary pursuit. Partnering with PhD colleagues and other disciplines led to eventual success.

Thus, it may be worthwhile to piggyback with other successful researchers before you pursue independence. The average age for an RO1 grant in urology is well past 50. To sustain your interest in research until then, you need to find pathways to have clinical dollars or institutional support.

**Failure to learn outcomes**

My biggest regret is not personally keeping track of my surgical experience from the beginning. So many opportunities were lost in not being able to show trends, measure outcomes, and publish a plethora of data from prospective records. Retrospective studies are dissatisfying and poor in quality. When starting, no one envisions the need for data and in hindsight there are many regrets. Through helping establish the AUA AQUA Registry, I wish to avail others of the opportunity.

**Failure to be objective in device trials**

Being asked to be a principal investigator or participate in a device trial is seductive, whereas not being asked is dispiriting and depressing. In academic life, you want to be on the cutting edge. Failure lies in not being objective and not being critical early in trials. Everyone in the group wants to be positive, as being critical can be viewed as not being a team player or worse, being taken off the team.

As I look back, the number of trials that never brought a product to market or did not survive was considerable. I gained a valuable lesson, which was to be honest with the results and present/publish negative data. Credibility is way more important than a publication that is discredited later. My relationships with other trial participants, industry, and clinical coordinators were a major plus in virtually every trial in which I participated.

The list of trials that did not make it to the market or disappeared is much longer list than the list of those that remain successful. Endopyelotomy, the UroLume device, balloon dilation of the prostate, alcohol injection of the prostate, bulking agents, and cell therapy all have a string of publications attached to them. Mesh use has consumed my last decade. By my own account, I have more publications on trials that are no longer around.

**Failure to assist in the desire to lead**

As surgeons, we want to operate. It took some knocks early in my surgical career to learn the valuable lesson that the best surgeon is the one who can assist with and anticipate the next step of the primary surgeon. It is also true in the academic community, be it in the department or in the society, that working behind the scenes is not considered valuable, as everyone seeks a title.

I have seen too often a lack of vision or efficacy after obtaining the title if you have not paid your dues. Surgical training is the same, as the basic tenet of assisting is lost in the millennial pursuit of duty hours and not wanting to be a second assist for the sake of learning.

**Failure to recognize those who make you look good**

Again, the team science exists not only in research but in daily work. All around you are people who you do not acknowledge.

Please see SUCCESS, page 11.
ADT’s benefit studied in post-RP men undergoing salvage RT

Increased ADT duration cuts recurrence risk in men with two or more risk factors

Biochemical recurrence after radical prostatectomy (RP) may occur in 20% to 50% of cases and salvage radiation therapy (SRT) is considered the best treatment in most cases. But the questions about whether to add androgen deprivation therapy (ADT), as well as its dose and duration, remain subjects of active clinical debate.

Two previously published studies have demonstrated either improved overall survival or progression-free survival in men treated with a combination of SRT with ADT. At the same time, there is increasing awareness about significant adverse effects associated with the use of ADT, which can result in worse quality of life. The rate and severity of these side effects depend on the ADT duration.

In a recent report by Fossati et al, the authors aimed to study the impact of SRT plus ADT on clinical recurrence in relation to the duration of ADT and tumor characteristics (Eur Urol Feb. 21, 2019 [Epub ahead of print]).

The study included 1,264 patients from eight tertiary referral centers, between 1996 and 2012, who received SRT to the prostatic and seminal vesicle bed, with or without concomitant ADT. These patients had pathologic stage T2-4, N0-Nx, M0-Mx. Most of the patients (1,125, 89%) received SRT for rising PSA, while others were treated due to persistent PSA (139, 11%) after surgery.

The median dose of SRT was 66 Gy (interquartile range, 63-66 Gy). Whole-pelvis SRT was administered to 430 patients (24%). The decision to irradiate the pelvic lymph nodes and the type, dose, and duration were left to the discretion of treating physicians.

After a median follow-up of 93 months, 182 patients developed clinical recurrence (CR), defined as local recurrence, pelvic or retroperitoneal lymph node recurrence, or visceral or skeletal metastases noted on radiologic studies. The estimated CR-free survival rate at 8-year follow-up was 92%. Multivariable analysis revealed that concomitant ADT duration was inversely associated with the risk of CR (hazard ratio per 2 mos: 0.95, 95% CI: 0.92-0.99; p = .022).

Further, pathologic stage ≥pT3b (HR: 3.79; p < .0001), pathologic Gleason score ≥8 (HR: 1.99; p < .0005), and PSA level ≥0.5 at RT (HR: 1.18; p = .015) were associated with increased risk of CR after SRT±ADT.

Of these three risk factors, 531 patients (42%) had zero, 507 (40%) had one, and 226 (18%) had two or more risk factors. The estimated 8-year Kaplan-Meyer CR-free survival rate was 94%, 89%, and 71% for men with zero, one, and two or more risk factors, respectively (p < .0001).

In men with two or more risk factors, increasing duration of concomitant ADT (up to 36 months) was beneficial in reducing the risk of CR by nearly one-half in the first 12 months and an additional 25% by 18 months of ADT. In men with only one risk factor, there was some benefit noted when ADT was used for ≤12 months but not with longer duration of ADT. Finally, in men without any of these three risk factors, the risk of CR was low and did not improve with concomitant ADT.

Interestingly, surgical margin status, which has demonstrated variable prognostic value, was not used as one of the main risk factors. This multicenter retrospective study is not able to provide guidance regarding the best dose of SRT or the type of hormonal suppression associated with the lowest risk of CR. The authors also do not report on the location of CR in men with variable risk factor; ie, in-field (prostate bed, pelvic lymph nodes) or out-of-field (visceral or skeletal). It would be of great interest to know the pattern of CR, which can inform clinical decision-making to develop new or modified treatment regimens.

This study provides clinically useful information about when to use concomitant ADT and for how long. Even a short course of ADT can be associated with prolonged adverse effects in some men. Thus, safely avoiding hormonal suppression should be the goal in all men with prostate cancer, whether it is during primary or salvage radiation therapy.
**Posterior Reversible Encephalopathy Syndrome (PRES)**

XTANDI in patients who develop a seizure during treatment. Seizure can cause serious harm to themselves or others. Permanently discontinue XTANDI and of engaging in any activity where sudden loss of consciousness could occur. In a study of patients with predisposing factors for seizure, 2.2% of XTANDI-treated patients experienced a seizure. Patients in the study had one or more of the following pre-disposing factors: use of medications that may lower the seizure threshold; history of traumatic brain or head injury, cerebrovascular accident or transient ischemic attack, Alzheimer’s disease, meningioma, or leptomeningeal disease from prostate cancer, unexplained loss of consciousness within the last 12 months, history of ischemic heart disease, cerebrovascular accident or transient ischemic attack, Alzheimer’s disease. In one or more of the following pre-disposing factors: use of medications that may lower the seizure threshold; history of traumatic brain or head injury, cerebrovascular accident or transient ischemic attack, Alzheimer’s disease, meningioma, or leptomeningeal disease from prostate cancer, unexplained loss of consciousness within the last 12 months, history of ischemic heart disease, cerebrovascular accident or transient ischemic attack, Alzheimer’s disease, meningioma, or leptomeningeal disease from prostate cancer.

**Ischemic Heart Disease** In the placebo-controlled clinical studies, ischemic heart disease occurred more commonly in patients on the XTANDI arm compared to patients on the placebo arm (2.7% vs 1.2%). Grade 3-4 ischemic events occurred in 1.2% of patients on XTANDI versus 0.5% on placebo. Ischemic events led to death in 0.4% of patients on XTANDI compared to 0.1% on placebo. Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue XTANDI for Grade 3-4 ischemic heart disease.

**Falls and Fractures** In the placebo-controlled clinical studies, falls occurred in 10% of patients treated with XTANDI compared to 4% of patients treated with placebo. Fractures occurred in 8% of patients treated with XTANDI and in 3% of patients treated with placebo. Evaluate patients for fracture and fall risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

**Embryo-Fetal Toxicity** Safety and efficacy of XTANDI have not been established in females. XTANDI can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment with XTANDI and for 3 months after the last dose of XTANDI. XTANDI should not be handled by females who are or may become pregnant.

**Adverse Reactions** The most common adverse reactions (≥ 10%) that occurred more frequently (≥ 2% over placebo) in the XTANDI patients from the randomized placebo-controlled trials were asthenia/fatigue, decreased appetite, hot flush, arthralgia, dizziness/vertigo, hypertension, headache and weight decreased. In the bicalutamide-controlled study, the most common adverse reactions (≥ 10%) reported in XTANDI patients...
XTANDI significantly prolonged metastasis-free survival in patients with nonmetastatic CRPC and significantly extended overall survival and radiographic progression-free survival in patients with metastatic CRPC.

Nonmetastatic CRPC: Median metastasis-free survival was 3 years (36.6 months [95% CI, 33.1-NC]) with XTANDI + LHRH therapy vs 14.7 months (95% CI, 14.2-15.0) with placebo + LHRH therapy (HR = 0.29 [95% CI, 0.24-0.35]; P < 0.0001).†

Metastatic CRPC: 23% reduction in the risk of death with XTANDI + LHRH therapy vs placebo + LHRH therapy (HR = 0.77 [95% CI, 0.67-0.88]) and 83% reduction in the risk of radiographic progression or death vs placebo + LHRH therapy (HR = 0.17 [95% CI, 0.14-0.21]; P < 0.0001).§

As seen in the PROSPER trial: a multinational, randomized, double-blind phase 3 trial that enrolled 1401 patients with nonmetastatic CRPC who progressed on LHRH therapy. Eligibility criteria included PSA doubling time ≤ 10 months and no prior chemotherapy.¶

As seen in the PREVAIL trial: a multinational, randomized, double-blind phase 3 trial that enrolled 1717 patients with metastatic CRPC who progressed on LHRH therapy. Eligibility criteria included no prior chemotherapy.¶

Drug Interactions

Effect of Other Drugs on XTANDI: Avoid strong CYP2C8 inhibitors, as they can increase the plasma exposure to XTANDI. If co-administration is necessary, reduce the dose of XTANDI.

Avoid strong CYP3A4 inducers as they can decrease the plasma exposure to XTANDI. If co-administration is necessary, increase the dose of XTANDI.

Effect of XTANDI on Other Drugs: Avoid CYP3A4, CYP2C9, and CYP2C19 substrates with a narrow therapeutic index, as XTANDI may decrease the plasma exposures of these drugs. If XTANDI is co-administered with warfarin (CYP2C9 substrate), conduct additional INR monitoring.

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

Initial U.S. Approval: 2012

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

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

**INDICATIONS AND USAGE**

XTANDI® (enzalutamide) capsules for oral use are indicated for the treatment of patients with castration-resistant prostate cancer.

**CONTRAINdications**

None.

**WARNINGS AND PRECAUTIONS**

Seizure

Seizure occurred in 0.4% of patients receiving XTANDI in clinical studies. In these trials, patients with predisposing factors for seizure were generally excluded. Seizures occurred from 13 to 604 days after initiation of XTANDI. Patients experiencing seizure were permanently discontinued from therapy and all seizure events resolved.

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

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

**Posterior Reversible Encephalopathy Syndrome (PRES)**

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

**Hypersensitivity**

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

Permanently discontinue XTANDI for serious hypersensitivity reactions.

**Ischemic Heart Disease**

In the combined data of three randomized, placebo-controlled clinical studies, ischemic heart disease occurred more commonly in patients on the XTANDI arm compared to patients on the placebo arm (2.7% vs 1.2%). Grade 3-4 ischemic events occurred in 1.2% of patients in the XTANDI arm compared to 0.5% in the placebo arm. Ischemic events led to death in 0.4% of patients in the XTANDI arm compared to 0.1% in the placebo arm.

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

**Falls and Fractures**

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

In the combined data of three randomized, placebo-controlled clinical studies, falls occurred in 10% of patients treated with XTANDI compared to 4% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Fractures occurred in 8% of patients treated with XTANDI and in 3% of patients treated with placebo. Grade 3-4 fractures occurred in 2% of patients treated with XTANDI and in < 1% of patients treated with placebo. The median time to onset of fracture was 337 days (range: 2 to 996 days) for patients treated with XTANDI. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the studies.

**Embryo-Fetal Toxicity**

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

**ADVERSE REACTIONS**

**Clinical Trial Experience**

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

Four randomized controlled clinical trials enrolled patients with CRPC that had progressed on ADT. Patients received XTANDI 160 mg (2784 patients) or placebo orally once daily (1708 patients) or bicalutamide 50 mg orally once daily (189 patients). All patients continued androgen deprivation therapy (ADT).

The most common adverse reactions (> 10%) that occurred more frequently (> 2% over placebo) in the XTANDI-treated patients from the randomized placebo-controlled clinical trials were asthenia/ fatigue, decreased appetite, hot flush, arthralgia, dizziness/vertigo, hypertension, headache, and weight decreased.

**AFFIRM (NCCT00747311): XTANDI versus Placebo in Metastatic CRPC Following Chemotherapy**

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

Grade 3 and higher adverse reactions were reported among 47% of XTANDI-treated patients and 53% of placebo-treated patients. Discontinuations due to adverse events were reported for 16% of XTANDI-treated patients and 18% of placebo-treated patients. The most common adverse reaction leading to treatment discontinuation was seizure, which occurred in 0.9% of the XTANDI-treated patients compared to none (0%) of the placebo-treated patients.

Table 1 shows adverse reactions reported in AFFIRM that occurred at ≥ 2% higher frequency in the XTANDI arm compared to the placebo arm.

**Table 1. Adverse Reactions in AFFIRM**

<table>
<thead>
<tr>
<th>Condition</th>
<th>XTANDI N = 800</th>
<th>Placebo N = 399</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1-2 (%)</td>
<td>Grade 3-4 (%)</td>
<td>Grade 1-2 (%)</td>
</tr>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenic Conditions²</td>
<td>51</td>
<td>90</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>15</td>
<td>1.0</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back Pain</td>
<td>26</td>
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</tr>
<tr>
<td>Arthralgia</td>
<td>21</td>
<td>2.5</td>
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<tr>
<td>Musculoskeletal Pain</td>
<td>15</td>
<td>1.3</td>
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<tr>
<td>Muscular Weakness</td>
<td>9.8</td>
<td>1.5</td>
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<tr>
<td>Neuropathic Weakness</td>
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<td>0.3</td>
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<tr>
<td>Gastrointestinal Disorders</td>
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<tr>
<td>Diarrhea</td>
<td>22</td>
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<tr>
<td>Vascular Disorders</td>
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<tr>
<td>Hot Flush</td>
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<tr>
<td>Hypertension</td>
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<td>2.1</td>
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<tr>
<td>Nervous System Disorders</td>
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<tr>
<td>Fractures</td>
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<td>0.9</td>
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<tr>
<td>Dizziness²</td>
<td>9.5</td>
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<tr>
<td>Spinal Cord Compression</td>
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<td>6.6</td>
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<tr>
<td>Syndrome</td>
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<td>Hypertension</td>
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<td>Tinnitus</td>
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<td>Hypoesthesia</td>
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<tr>
<td>Infections and Infestations</td>
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<tr>
<td>Upper Respiratory Tract Infection³</td>
<td>11</td>
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<tr>
<td>Lower Respiratory Tract and Lung Infection</td>
<td>8.5</td>
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<td>Psychiatric Disorders</td>
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<td>Insomnia</td>
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<td>Anxiety</td>
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<td>Renal and Urinary Disorders</td>
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<td>Hematuria</td>
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<td>Pollakiuria</td>
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<td>Injury, Poisoning and Procedural Complications</td>
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<td>Fall</td>
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<td>Non-pathologic Fractures</td>
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<td>Skin and Subcutaneous Tissue Disorders</td>
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<tr>
<td>Dry Skin</td>
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<td>0.0</td>
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<td>Respiratory Disorders</td>
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</tr>
<tr>
<td>Epistaxis</td>
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</tr>
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</table>

1. CTCAE v4
2. Includes asthma and fatigue.
3. Includes dizziness and vertigo.
4. Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention.
5. Includes nephropathy, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis.
6. Includes pneumonia, lower respiratory tract infection, bronchitis, and lung infection.
PREVAIL (NCT01212991): XTANDI versus Placebo in Chemotherapy-naive Metastatic CRPC

PREVAIL enrolled 1717 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 1715 received at least one dose of study drug. The median duration of treatment was 17.5 months with XTANDI and 4.6 months with placebo. Grade 3-4 adverse reactions were reported in 44% of XTANDI-treated patients and 37% of placebo-treated patients. Discontinuations due to adverse events were reported for 6% of XTANDI-treated patients and 6% of placebo-treated patients. The most common adverse reaction leading to treatment discontinuation was fatigue/asthenia, which occurred in 1% of patients on each treatment arm. Table 2 includes adverse reactions occurring in 1% of patients on each treatment arm. Table 2 shows overall and common adverse reactions (>10%) in XTANDI-treated patients.

**Table 2. Adverse Reactions in PREVAIL**

<table>
<thead>
<tr>
<th>Reaction Category</th>
<th>XTANDI N = 871</th>
<th>Placebo N = 844</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenic Conditions</td>
<td>47 (3.4)</td>
<td>33 (2.8)</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>12 (0.2)</td>
<td>8.2 (0.4)</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back Pain</td>
<td>29 (2.5)</td>
<td>22 (3.0)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>21 (1.6)</td>
<td>16 (1.1)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>23 (2.7)</td>
<td>17 (2.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17 (2.0)</td>
<td>13 (1.5)</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot Flush</td>
<td>18 (2.1)</td>
<td>7.8 (0.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (1.7)</td>
<td>4.1 (2.3)</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>11 (1.3)</td>
<td>7.1 (0.9)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (1.2)</td>
<td>7.0 (0.4)</td>
</tr>
<tr>
<td>Dysphoria</td>
<td>7.6 (0.1)</td>
<td>57.0 (0.0)</td>
</tr>
<tr>
<td>Mental Impairment Disorders</td>
<td>5.7 (0.0)</td>
<td>13.0 (0.1)</td>
</tr>
<tr>
<td>Restless Legs Syndrome</td>
<td>2.1 (0.1)</td>
<td>4.0 (0.4)</td>
</tr>
<tr>
<td>Respiratory Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>11 (1.6)</td>
<td>8.5 (0.6)</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>16 (0.0)</td>
<td>11.0 (0.0)</td>
</tr>
<tr>
<td>Lower Respiratory Tract and Lung Infection</td>
<td>7.9 (1.5)</td>
<td>4.7 (1.1)</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>8.2 (0.1)</td>
<td>5.7 (0.0)</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td>8.8 (1.3)</td>
<td>5.8 (1.3)</td>
</tr>
<tr>
<td>Injury, Poisoning and Procedural Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>13 (1.6)</td>
<td>53.0 (0.7)</td>
</tr>
<tr>
<td>Non-Pathological Fracture</td>
<td>8.8 (2.1)</td>
<td>3.0 (1.1)</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>19 (0.3)</td>
<td>16 (0.7)</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Decreased</td>
<td>12 (0.8)</td>
<td>8.5 (0.2)</td>
</tr>
</tbody>
</table>

**Table 2. Adverse Reactions in PREVAIL**

<table>
<thead>
<tr>
<th>Reaction Category</th>
<th>XTANDI N = 183</th>
<th>Bicalutamide N = 189</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenic Conditions</td>
<td>32 (1.6)</td>
<td>23 (1.1)</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back Pain</td>
<td>19 (2.7)</td>
<td>18 (1.6)</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot Flush</td>
<td>15 (0.0)</td>
<td>11 (0.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (7.1)</td>
<td>4.2 (4.2)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>14 (0.0)</td>
<td>18 (0.0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>13 (1.1)</td>
<td>13 (0.5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (0.0)</td>
<td>9.0 (1.1)</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>12 (0.0)</td>
<td>6.3 (0.5)</td>
</tr>
<tr>
<td>Investigational</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Loss</td>
<td>11 (0.5)</td>
<td>7.9 (0.5)</td>
</tr>
</tbody>
</table>

**Table 3. Adverse Reactions in TERRAIN**

<table>
<thead>
<tr>
<th>Reaction Category</th>
<th>XTANDI N = 375</th>
<th>Bicalutamide N = 372</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>37 (5.6)</td>
<td>27 (7.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>14 (2.4)</td>
<td>6.6 (1.8)</td>
</tr>
<tr>
<td>Dysphoria</td>
<td>16 (4.0)</td>
<td>5.9 (1.6)</td>
</tr>
<tr>
<td>Mental Impairment Disorders</td>
<td>5.7 (0.0)</td>
<td>13.0 (0.1)</td>
</tr>
<tr>
<td>Restless Legs Syndrome</td>
<td>2.1 (0.1)</td>
<td>4.0 (0.4)</td>
</tr>
<tr>
<td>Respiratory Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>11 (2.9)</td>
<td>16.9 (0.8)</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>16 (0.0)</td>
<td>11.0 (0.0)</td>
</tr>
<tr>
<td>Lower Respiratory Tract and Lung Infection</td>
<td>7.9 (1.5)</td>
<td>4.7 (1.1)</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>8.2 (0.1)</td>
<td>5.7 (0.0)</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td>8.8 (1.3)</td>
<td>5.8 (1.3)</td>
</tr>
<tr>
<td>Injury, Poisoning and Procedural Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>13 (1.6)</td>
<td>53.0 (0.7)</td>
</tr>
<tr>
<td>Non-Pathological Fracture</td>
<td>8.8 (2.1)</td>
<td>3.0 (1.1)</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>19 (0.3)</td>
<td>16 (0.7)</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Decreased</td>
<td>12 (0.8)</td>
<td>8.5 (0.2)</td>
</tr>
</tbody>
</table>

**PROSPER (NCT02003924): XTANDI versus Placebo in Non-metastatic CRPC Patients**

PROSPER enrolled 1401 patients with non-metastatic CRPC, of whom 1396 received at least one dose of study drug. Patients were randomized 2:1 and received either XTANDI at a dose of 160 mg once daily (N = 930) or placebo (N = 465). The median duration of treatment at the time of analysis was 18.4 months (range 0.0 to 42 months) with XTANDI and 11.1 months (range 0.0 to 43 months) with placebo. Overall, 32 patients (3.4%) receiving XTANDI died from adverse events. The reasons for death with ≥ 2 patients included coronary artery disorders (n = 7), sudden death (n = 2), cardiac arrhythmias (n = 2), general physical health deterioration (n = 2), stroke (n = 1), and secondary malignancy (n = 5); one each of acute myeloid leukemia, brain neoplasm, mesothelioma, small cell lung cancer, and malignant neoplasm of unknown primary site). Three patients (0.6%) receiving placebo died from adverse events of cardiac arrest (n = 1), left ventricular failure (n = 1), and pancreatic carcinoma (n = 1). Grade 3 or higher adverse reactions were reported among 31% of XTANDI-treated patients and 23% of placebo-treated patients. Discontinuations due to adverse events in XTANDI arm. Table 2 shows overall and common adverse reactions (>10%) in XTANDI-treated patients.

**Table 4. Adverse Reactions in PROSPER**

<table>
<thead>
<tr>
<th>Reaction Category</th>
<th>XTANDI N = 930</th>
<th>Placebo N = 465</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>9.6 (0.2)</td>
<td>3.9 (0.2)</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>12 (0.5)</td>
<td>5.2 (0.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>9.1 (0.2)</td>
<td>4.5 (0.0)</td>
</tr>
<tr>
<td>Cognitive and Attention Disorders</td>
<td>4.6 (1.5)</td>
<td>1.0 (0.0)</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot Flush</td>
<td>13 (0.1)</td>
<td>7.7 (0.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (4.6)</td>
<td>5.2 (2.2)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (1.0)</td>
<td>8.6 (0.0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>9.1 (0.2)</td>
<td>6.9 (0.0)</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenic Conditions</td>
<td>40 (4.0)</td>
<td>20 (0.9)</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Decreased</td>
<td>5.9 (0.2)</td>
<td>1.5 (0.0)</td>
</tr>
<tr>
<td>Injury, Poisoning and Procedural Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fractures</td>
<td>9.8 (2.0)</td>
<td>4.9 (1.7)</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>2.5 (0.2)</td>
<td>4.0 (0.4)</td>
</tr>
</tbody>
</table>

**Laboratory Abnormalities**

In the AFFIRM and PREVAIL studies in metastatic CRPC, Grade 1-4 neutropenia occurred in 15% of patients receiving XTANDI (Grade 3-4) and in 6% of patients receiving placebo (0.5% Grade 3-4).

Table 5 shows laboratory abnormalities that occurred in ≥ 5% of patients, and more frequently (>2%) in the XTANDI arm compared to placebo in the PROSPER study.

**Table 5. Laboratory Abnormalities in PROSPER**

<table>
<thead>
<tr>
<th>Reaction Category</th>
<th>XTANDI N = 930</th>
<th>Placebo N = 465</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>8.2 (0.5)</td>
<td>5.4 (0.2)</td>
</tr>
<tr>
<td>Hypoanemia</td>
<td>16 (1.3)</td>
<td>8.8 (0.5)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>7.8 (2.9)</td>
<td>7.3 (1.3)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>26 (0.0)</td>
<td>21 (0.0)</td>
</tr>
</tbody>
</table>
Hypertension
In the AFFIRM and PREVAIL studies in metastatic CRPC, hypertension was reported in 11% of patients receiving XTANDI and 4% of patients receiving placebo. Medical history of hypertension was balanced between arms. Hypertension led to study discontinuation in 1% of patients in each arm. In the PROSPER study in non-metastatic CRPC, hypertension was reported in 12% of patients receiving XTANDI and 5% of patients receiving placebo.

Post-Marketing Experience
The following additional adverse reactions have been identified during post-approval use of XTANDI. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency of occurrence or establish a causal relationship to drug exposure.

Body as a Whole: hypsersensitivity (edema of the face, tongue, lip, or pharynx)

Gastrointestinal Disorders: vomiting

Neurological Disorders: posterior reversible encephalopathy syndrome (PRES)

Drug Interactions

Drugs that Inhibit CYP2C8
Co-administration of a strong CYP2C8 inhibitor (gemfibrozil) increased the composite area under the curve (AUC) of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold. Co-administration of XTANDI with strong CYP2C8 inhibitors should be avoided if possible. If co-administration of XTANDI with a strong CYP2C8 inhibitor cannot be avoided, reduce the dose of XTANDI.

Drugs that Induce CYP3A4
Co-administration of rifampin (strong CYP3A4 inducer and moderate CYP2C8 inducer) decreased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 37%. Co-administration of strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampin, rifabutin, rifapentine) with XTANDI should be avoided if possible. St John’s wort may decrease enzalutamide exposure and should be avoided. If co-administration of a strong CYP3A4 inducer with XTANDI cannot be avoided, increase the dose of XTANDI.

Effect of XTANDI on Drug Metabolizing Enzymes
Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. At steady-state, XTANDI reduced the plasma exposure to midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate). Concomitant use of XTANDI with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, imipramine, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephenytoin, clopidogrel) should be avoided, as enzalutamide may decrease the exposure of these drugs. If co-administration with warfarin cannot be avoided, conduct additional INR monitoring.

Use in Specific Populations

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

Animal Data
In an embryo-fetal developmental toxicity study in mice, enzalutamide caused developmental toxicity when administered at oral doses of 10 or 30 mg/kg/day throughout the period of organogenesis (gestational days 6-15). Findings included embryo-fetal lethality (increased post-implantation loss and resorptions) and decreased anogenital distance at ≥ 10 mg/kg/day, and cleft palate and absent patine bone at ≥ 30 mg/kg/day. Doses of 30 mg/kg/day caused maternal toxicity. The doses tested in mice (1, 10 and 30 mg/kg/day) resulted in systemic exposures (AUC) approximately 0.4, 0.4 and 1.1 times, respectively, the exposures in patients. Enzalutamide did not cause developmental toxicity in rabbits when administered throughout the period of organogenesis (gestational days 6-19) at doses of 10 mg/kg/day (approximately 0.4 times the exposures in patients based on AUC).

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

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

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

Females and Males of Reproductive Potential

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

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

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

Geriatric Use
2784 patients who received XTANDI in four phase 3 clinical trials in patients with metastatic CRPC and healthy volunteers, no significant difference in enzalutamide clearance was observed in patients with pre-existing mild to moderate renal impairment (30 mL/min ≤ creatinine clearance [CrCl] < 60 mL/min) compared to patients and volunteers with baseline normal renal function (CrCl ≥ 90 mL/min). No initial dosage adjustment is necessary for patients with mild to moderate renal impairment. Severe renal impairment (CrCl < 30 mL/min) and end-stage renal disease have not been assessed.

Patients with Hepatic Impairment

Dedicated hepatic impairment trials compared the composite systemic exposure of enzalutamide plus N-desmethyl enzalutamide in volunteers with baseline mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C, respectively) versus healthy controls with normal hepatic function. The composite AUC of enzalutamide plus N-desmethyl enzalutamide was similar in volunteers with mild, moderate, or severe baseline hepatic impairment compared to volunteers with normal hepatic function. No initial dosage adjustment is necessary for patients with baseline mild, moderate, or severe hepatic impairment.

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Administration of enzalutamide to male and female rats with transgenic mice by oral gavage daily for 26 weeks did not result in increased incidence of neoplasms at doses up to 20 mg/kg/day. Enzalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either the in vitro mouse lymphoma thymidine kinase (TK) gene mutation assay or the in vivo mouse micronucleus assay.

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

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Marketed by: Astellas Pharma US, Inc., Northbrook, IL 60062

Pfizer Inc., New York, NY 10017

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076-3717-PM
Emerging treatment options for ED: Hope or hype?

Novel therapies are promising but face questions about patient selection, efficacy.

**Dopaminergic agents.** Initially, the use of dopamine agonists for Parkinson’s disease was associated with increased libido. Apomorphine is a dopamine D1 and D2 receptor agonist that was approved for ED in Europe in 2001. In a phase III double-blind, parallel-arm, crossover study of nearly 900 men with ED, more than 50% of those using apomorphine were able to obtain an erection sufficient for intercourse compared to 33% of men using placebo (BJU Int 2002; 89:409-415). However, the FDA did not approve the drug in the United States because of concerns about hypotension. Similar medications (ABT-724 and ABT-670) targeted to the D4 receptor have also been studied, but development was stopped after phase II studies.

**Melanocortin receptor agonists.** Melanocortin receptor agonists including melanotan II (subcutaneous administration) and bremmelanotide (intranasal administration) have been studied for ED. Both formulations improved erectile function in studied men, although they were poorly tolerated in clinical studies. Patients given melanotan II experienced severe emesis, and bremmelanotide caused severe hypertension. Further clinical development has been discontinued. Recently, a landmark study identified a single locus near the SIM1 gene that was associated with risk of ED independence.

Please see **ED TREATMENTS**, page 18.

**FIGURE / Cellular pathways in erectile function**

Abbreviations: CNS: Central nervous system; NO: nitric oxide; GC: guanylyl cyclase; GTP: guanosine triphosphate; cGMP: cyclic guanosine monophosphate; PDE5: phosphodiesterase type-5; PDE5i: phosphodiesterase type-5 inhibitor.

(Diagram courtesy of Darshan P. Patel, MD, Philip J. Cheng, MD, James M. Hotaling, MD, MS, and Alexander W. Pastuszak, MD, PhD)
ED TREATMENTS

continued from page 17

pended of known risk factors in a large cohort (Proc Natl Acad Sci USA 2018; 115:11018-23). SIM1 encodes transcription factors involved in the leptin-melanocortin pathway and may rep- sent an exciting target for future novel therapies.

Guanylyl cyclase activators. Soluble guanylyl cyclase is a key component of the nitric oxide (NO) pathway (figure). In post-prostatectomy patients or diabetics who have severe endothelial dysfunction and cavernous nerve injury, PDE-5 inhibition does not increase endogenous NO lev- els sufficiently. In these patients, direct activation of soluble guanylyl cyclase may enhance erections.

In a study of human cavernosal tissue obtained from patients during penile prosthesis implantation, compared to patients undergoing transurethral surgery, a combination of varde- nafil and guanylyl cyclase activator enhanced cavernosal smooth muscle relaxation (J Sex Med 2013; 10:1268-77). Unfortunately, this medica- tion has not progressed past phase II studies.

Rho kinase pathway. The RhoA/Rho kinase pathway contributes to cavernosal smooth muscle contraction, which is independent of the NO pathway. When activated, the smooth muscle myosin light chain (MLC) is phosphorylated by inhibiting MLCK, phosophatase, leading to calcium sensi- tization and smooth muscle contraction. Studies of hypertensive and diabetic rats have suggested upregulation of this pathway and a resultant worsening of erectile function. SAR407899 is a specific RhoA/Rho kinase inhibitor that induces penile erection with greater potency and longer duration than sildenafil in a diabetic rabbit model, as well as in human cavernosal tissue strips (J Transl Med 2012; 10:59). However, development of this drug ceased after completion of phase II clinical trials, without reporting of results.

Topical agents

Topical agents for the treatment of ED are an appealing alternative for patients who experience adverse effects with the use of oral PDE-5 inhibi- tors and who do not desire more invasive treat- ments. Topical alprostadil has been studied in sev- eral double-blind, placebo-controlled trials with notable improvements in International Index of Erectile Function (IIEF) scores and few minor side effects such as erythema at the administration site.

Topical sildenafil is currently being studied for the treatment of ED. A phase I pharmacokinetic and safety trial has shown good penetration of topi- cal sildenafil without significant side effects (bit. ly/topical-sildenafil). A phase II proof-of-concept study has been completed, although results have not yet been reported. Various formulations of both topical alprostadil and sildenafil are available through online outlets and compounding phar- macies, although tissue penetration and efficacy are likely variable. While promising, considerable investigation of topical agents is still needed.

Stem cells

Stem cells have become an attractive therapy for ED, particularly following prostatectomy, where ED is secondary to cavernosal nerve damage. Stem cells for the treatment of ED have been derived from a number of sources, including adipose tissue, bone marrow, urine, pla- centa, umbilical vein endothelium, and amniotic fluid. Adipose-derived stem cells are the most studied in ED treatment in the rat model, with several studies showing an improvement in intracavernosal pressure in rats injected with stem cells directly into the corpus cavernosum.

Additionally, combination treatment with brain-derived neurotrophic factor (BDNF), PDE-5 inhibitors, and adipose-derived stem cells have suggested a synergistic effect in improving erectile function in the rat model (Tissue Eng Part A 2014; 20:2446-54). However, data examining the therapeutic efficacy and safety of stem cells for treatment of ED in humans are limited, and this therapy remains experimental.

Platelet-rich plasma

Platelets play an important role in inflamma- tion, tissue remodeling, and angiogenesis. The use of autologous platelet-rich plasma (PRP) has been explored in the treatment of a num- ber of conditions, including ED. Whole blood is obtained from the patient through veni- puncture and the sample is then centrifuged to remove white and red blood cells. The super- natant contains platelets and plasma proteins, including growth factors and other components.

NUTRACEUTICALS FOR ED AT A GLANCE

Nutraceuticals are therapies that use alternative, natural, or herbal additives with claims of health ben- efits. Consumption of these therapies has exploded over the last decade. As a result of the Dietary Sup- plement Health Act of 1994, supplements are regulated as foods rather than medications. The aver- sion that men with ED often have to seeking medical care, in part from the negative stigma associated with the condition, has likely fueled this growing market.

Many nutraceuticals are commercially available without prescription and include up to a dozen different ingredients, including yohimbine, L-arginine, red ginseng, and Epimedium spp (or horny goat weed). However, the efficacy and bioavailability of these ingredients and formulations have not been well established. As such, the use of nutraceuticals for ED should be approached with caution.

Yohimbine. Yohimbine is derived from the African yohimbe tree and inhibits central alpha-2 adrenergic receptors to increase libido, although the true mechanism contributing to erections is unknown. An ear- lier meta-analysis suggested yohimbine had therapeutic efficacy with few adverse effects. More recent- ly, a study explored on-demand L-arginine glutamate and yohimbine in 45 patients with mild to mod- erate ED in a double-blind, placebo-controlled study (Eur Urol 2002; 41:608-13; discussion 13). Those who received the combination had improved erectile function domain responses on the International Index of Erectile Function (IIEF) compared to placebo. Yohimbine is the most promising nutraceutical, although it is uncertain how it compares to current oral ED medications.

L-arginine. L-arginine is a naturally occurring amino acid that is also a component of many nutra- ceuticals claiming to boost erectile function. It is a precursor to nitric oxide and supplementation with L-arginine can boost nitric oxide levels, leading to smooth muscle relaxation and increased blood flow. However, demonstrable efficacy of L-arginine supplementation is limited.

Red ginseng. Similar to L-arginine, ginseng affects the NO pathway, stimulating nitric oxide synthase (NOS). Nearly a dozen randomized studies have evaluated the use of ginseng for ED. Most have reported a positive effect, although each of these studies has methodologic flaws including selection bias, dosing, and follow-up. Adverse effects of red ginseng are generally mild and include headaches, gastrointestinal upset, skin irritation, and reports of symptomatic hypoglycemia in diabetics. However, currently there is no convincing evidence for therapeutic efficacy of this compound.

Epimedium spp (horny goat weed). Horny goat weed has gained popularity since it is easily market- able by its name. It is an extract from the epimedium flowering plant and contains the flavonol icariin, which has a mild PDE-5 inhibitor-like effect. Small animal studies have demonstrated an improvement in erectile function after administration of icariin. However, no human studies are available.
Let’s Talk Men’s Health

that can aid healing, which are then directly injected into the corpus cavernosum.

Wu et al performed intracavernosal injection of PRP in an animal model of ED after cavernous nerve crush injury, observing an improvement in erectile function after PRP (J Sex Med 2012; 9:2838-48). However, no studies evaluating the efficacy of PRP for ED in humans are currently available.

The safety of PRP has been suggested in a study by Matz et al in which PRP fibrin matrix was used in 16 patients for ED and/or Peyronie’s disease. There were no major complications, and minor complications included mild pain or bruising at the injection site in approximately 20% of patients (Investig Clin Urol 2018; 59:61-65). Although PRP is an interesting potential therapy for ED, further studies are warranted to evaluate its safety and efficacy.

Extracorporeal low-intensity shock wave therapy
Extracorporeal low-intensity shock wave therapy (LISWT) is an emerging treatment for ED. It has been studied previously for a number of other conditions, including tissue ischemia, wound healing, and musculoskeletal disorders. LISWT utilizes direct mechanical forces from a pulse energy source and indirect force through cavitation that is directed at the treatment target. For ED, LISWT is thought to induce microtrauma to the cavernosal tissue that upregulates angiogenic factors, resulting in new blood vessel growth.

Vardi et al were the first to systematically report their experience with LISWT for ED in 2010, and since then a number of other studies have been published suggesting some therapeutic efficacy, with minimal adverse effects (Eur Urol 2010; 58:243-8). However, the ability to draw conclusions from the current literature is limited due to difference in treatment protocols, follow-up time, and patient selection. Several ongoing randomized clinical trials will help our understanding of the role of LISWT in the treatment of ED.

Conclusions
Over the last decade, we have developed a better understanding of the pathophysiology of ED. However, novel therapies—especially oral agents—with demonstrable efficacy and favorable side effect profiles are lacking. Other innovative therapies in early clinical stages show promise, but there remain unanswered questions about patient selection and efficacy. Continued technological advances and a detailed understanding of the spectrum of pathophysiological mechanisms of ED will translate to novel therapies in the future.

### TABLE / ERECTILE DYSFUNCTION PATHWAYS FOR ORAL THERAPIES

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Source: Darshan P. Patel, MD, Philip J. Cheng, MD, James M. Hotaling, MD, MS, and Alexander W. Pastuszak, MD, PhD

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Features the Bundling Matrix

**Enter Codes**

- 52356
- 52276
- 52005
- 52234

**Click ‘Analyze Codes’**

**Then, the Matrix shows you, on one page:**

- Codes to bill
- Non-billable codes
- Codes that need modifiers

**52356**

- F: 12.05
- NF: 12.05
- RVU: 8
- Status: A
- Global: 000
- 03/28/2019

**Never Allowed**

(52356 includes 52005)

**OK to Bill**

**Modifier Required**

(52234 includes 52356)

**52005**

- F: 3.84
- NF: 8.05
- RVU: 2.37
- Status: A
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**OK to Bill**

**Modifier Required**

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- Status: A
- Global: 000
- 03/28/2019

**Modifier Required**

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**Conclusions**
Over the last decade, we have developed a better understanding of the pathophysiology of ED. However, novel therapies—especially oral agents—with demonstrable efficacy and favorable side effect profiles are lacking. Other innovative therapies in early clinical stages show promise, but there remain unanswered questions about patient selection and efficacy. Continued technological advances and a detailed understanding of the spectrum of pathophysiological mechanisms of ED will translate to novel therapies in the future.

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Can nurse practitioners see Medicare patients on their own?

NP’s national provider identifier can be used under several circumstances.

**Q:** Is a nurse practitioner allowed to see Medicare patients on their own? The “incident to” guidelines state that the physician must see the patient on the first visit to establish the physician-patient relationship; from there onward, the NP can see the patient under direct supervision. Can the NP see a new patient without the doctor being present?

**A:** We will answer this question with the obvious caveat that the state licensure for the advanced practice provider (APP) must allow for the NP to see new patients and render the services provided without a physician present.

Medicare payment rules allow the NP to provide patient services without patient-physician contact on the date of service.

**Medicare payment rules allow for the NP to provide patient services without patient-physician contact on the date of service.**

- The physician and NP both see the patient on the same date and documentation reflects that the physician was involved in the visit reconfirming findings and treatment plan for a new or established patient.
- An established patient is seen by the NP only and the treatment provided is a continuation of a treatment plan prescribed previously by a physician in the group (rendering provider is NPI of NP). The billing provider must be in the office suite at the time of this service (billing provider is NPI of physician present).
- For private payers, you will need to check your contracts or payer websites for appropriate billing and make sure that the NP is properly credentialed with each plan as required.
- Other services that are provided by the NP and ordered by the physician such as catheterization, injection, etc. can be reported under the “incident to” rules similar to nursing and other staff reporting.

**Q:** Can nurse practitioners see Medicare patients on their own? Do nurse practitioners have to be directly supervised by a physician?

**A:** Yes, nurse practitioners (NPs) are regulated by state laws. The “incident to” guidelines state that the physician must see the patient on the first visit to establish the physician-patient relationship; from there onward, the NP can see the patient under direct supervision. Can the NP see a new patient without the doctor being present?

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**Q:** We had a case in which the patient came into the clinic on day 1 for a vasectomy. The vasectomy was completed on the left side. However, we were unable to secure the right vas. A right-sided vasectomy was scheduled and completed at the local surgical center on day 2. How would you code, since 55250 is for unilateral or bilateral procedures?

**A:** We recommend reporting the first service with 55250-52 and the second service with 55250-58-52-76. Pricing for each should be decreased slightly from the normal case but does not need to be 50% as each side was somewhat complex.

Be sure to document in the first operative report the complexity of the problem and the plan to perform the second procedure to justify the use of the –58 modifier on the second procedure.

**Q:** Can 50543 be billed with 50541? The AUAcodingtoday.com bundling matrix notes that a modifier is needed, but we are unclear about which one. We did a partial nephrectomy on a 2-cm mass, but in order to even approach this mass and do the surgery, we had to remove an 8-cm renal cyst. We did a cyst decortication. This is a private payer, so is the –XU modifier correct or –59?

**A:** According to your comments, it would appear that the cyst was removed to facilitate the procedure. If so, you should not bill for the ablation of the cyst even though you performed a full decortication.

However, if the cyst ablation was medically necessary and not performed just to facilitate the primary procedure, then both could be charged: 50541 (Laparoscopy, surgical; ablation of renal cysts) is bundled into 50543 (Laparoscopy, surgical; partial nephrectomy); however, unbundling is allowed with an appropriate modifier.

The appropriate modifier would be –59 (Distinct Procedural Service) for private carriers unless that carrier has specifically stated that it recognizes the “X” modifiers. –XU (Unusual Non-Overlapping Service) should be appended for the Medicare patient.

**SEND US YOUR QUESTIONS**

Send coding and reimbursement questions to Ray Painter, MD, and Mark Painter c/o Urology Times, at UT@advanstar.com. 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.
How to leverage industry relationships while avoiding risks

Tracking samples, meeting with reps in non-care areas are key best practices

It is important to acknowledge that there is a role for industry-sponsored education of physicians, and that many busy urologists receive some or even most of their knowledge about new procedures, products, or new indications from industry sources.

The AUA has outlined principles to guide its members on interactions with industry (bit.ly/industryprinciples). Yet while the rules of engagement have become stricter, pharmaceutical companies continue to fund important clinical research, sponsor educational meetings not tied to their product, and try to develop direct customer relationships to build loyalty. While much has changed, much remains the same, especially in the area of pharmaceutical representatives in your office. In this article, I will examine some common issues in the office pertaining to industry reps and some possible solutions.

Drug samples. Pharma reps use samples to get access to physicians and influence prescribing habits (PLoS Med 2007; 4:e150). Urologists value drug samples because they can start treatment immediately at no cost, test how a patient will tolerate a drug, and give their patient a free present.

Samples create a liability for recordkeeping, inventory control, and patient safety. Consider the recent nationwide recall of a common blood pressure medication due to a cancer-causing impurity (bit.ly/medicationrecall). Would your practice be able to easily identify all of the patients who had been given a sample of, say, an overactive bladder medication? By lot number?

Best practices in this area include:
- Always enter the medication into your electronic health record, which will then perform important safety checks like drug-drug, drug-disease, and drug-allergy interactions as well as populate the patient’s medication list.
- Enter the lot number of any medications injected, administered, or sampled in the office—so the patient can be identified by lot number in the event of a recall.
- Provide the patient with printed instructions, warnings, and other information just as they would receive if they went to a retail pharmacy.
- Maintain an inventory log of samples, control access to those samples, and dispose of expired medications.

If you aren’t willing to follow these best practices, maybe it is time to consider whether the value of samples to your patients and your practice is worth the liability.

Education. It is important to acknowledge that there is a role for industry-sponsored education of physicians, and that many busy urologists receive some or even most of their knowledge about new procedures, products, or new indications from industry sources: sponsored meetings, manufacturer’s websites, prescribing literature, or even pharmaceutical salespeople and “leave-behinds.” Those same reps may be the sole source of training and education on new products for your clinical staff and assistants. Some device manufacturers separate the role of sales and training of physicians, and until recently a different set of rules characterized relationships between drug and device manufacturers and their physician customers.

Best practices in this area include:
- Do not finish your education of novel therapies and treatments with sales materials, but possibly begin there.
- Do not challenge pharmaceutical representatives about the accuracy of their claims—they likely know more than you do about any research that supports their product; supplement the information targeted at you with continuing education from an objective source.
- Supervise any education of your clinical staff and keep them aligned with your prescribing patterns and habits, minimizing the chance that your patients will hear different messages from you and your staff.

If you follow these best practices, you can realize the advantage of industry-sponsored education and avoid the pitfalls that could affect your professional practice.
INDUSTRY REPS
continued from page 21

Privacy. Most urology offices were not designed beyond the requirement for patient care, and many were not built to accommodate growth in volume and staff. The conditions are ripe in many practices for conversations to be overheard, for bystanders to be exposed to personal information, and even for proprietary information to be shared unintentionally.

A vendor representative is frequently a repeat guest who knows your front staff, brings food, and is welcomed through the reception room door into a busy corridor or checkout area where he or she is exposed directly to protected health information and the inner workings of your practice. Most are honest professionals who want to build trust and understand the sensitivity of the business of urology, but they are guests. They are not usually bound by a confidentiality agreement with you, and they may also call on your referrals to a guest; for example, how many patients you see, whether you are successfully getting reimbursed by a payer, or where your referrals come from or go to.

• Meet with industry outside of the clinical care area, and avoid exposing them to patients or their records altogether. 
• Do not discuss any proprietary information with a guest; for example, how many patients you see, whether you are successfully getting reimbursed by a payer, or where your referrals come from or go to. 
• Have industry representatives who may be exposed to proprietary information sign a confidentiality agreement, just as a third party who handles protected health information must sign a business associates agreement.

If you respect the privacy of your patients, your staff, and yourself, you will enjoy the professional respect of industry reps.

Follow these steps to mitigate your cybersecurity risk

Joseph E. Guimera, JD

Continuing cyberattacks on health care providers emphasize the need for medical practices of all sizes to make cybersecurity an essential part of their business. Here are steps you can take to strengthen your practice’s cybersecurity position.

Conduct a risk assessment. Successful cybersecurity begins with understanding the actual threats and vulnerabilities your practice faces. A cybersecurity risk assessment lists the practice assets that could be subject to cyberattack (such as hardware, systems, mobile devices, patient data, etc.), identifies the possible threats to those assets, and evaluates the likelihood of the identified threats actually occurring. This allows you to focus resources on the risks most likely to occur and prioritize which vulnerabilities to address first.

A risk assessment also is important in the event of a data breach. It shows you acted reasonably in identifying and addressing potential threats and may be required to obtain cybersecurity insurance.

Secure your systems. Unprotected systems and outdated programs and software are frequent points of attacks for cybercriminals. To safeguard your systems:

• Install antivirus and anti-malware software to scan email attachments for viruses and your system for malware. 
• Install a firewall to protect your network by monitoring and controlling the incoming and outgoing data streams. 
• Regularly update your programs and software. Promptly install all software updates since these often contain security patches addressing vulnerabilities discovered since the last update. 
• Encrypt your data. Several readily available programs allow you to encrypt a select group of files, or for a more secure option, your entire hard drive. 
• Regularly back up your data to a secure cloud platform, an external hard drive, or to both. Backups will enable you to recover your data in the event it is damaged, lost, stolen, or held hostage with ransomware.

Restrict access to data. Not every staff member needs, or should have, access to all of your practice’s data. Staff should have access only to data they need to properly perform their job functions. Determine access and privileges by following a three-tiered data classification system that restricts access according to data sensitivity.

To read the entire article, which was originally published by Urology Times sister brand Physicians Practice, go to bit.ly/medicalsecurityrisks.
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How the 2017 tax law will affect your filing this year

Standard deduction, child tax credit see increases under legislation

**Q:** With this being the first year the new tax law will impact how people file, what are some big changes I should pay attention to as I prepare my 2018 taxes?

**A:** At the end of 2017, the Tax Cuts & Jobs Act was passed by Congress and signed into law by President Trump. This tax season will be the first time many of the changes officially take effect. This article will provide an overview of some of the bigger changes that occurred.

The bill preserves seven tax brackets, but changes the rates that apply to 10%, 12%, 22%, 24%, 32%, 35%, and 37%. Here’s how much 2018 income applies to the new rates:
- 10% (income up to $9,525 for individuals; up to $19,050 for married couples filing jointly)
- 12% (over $9,525 to $38,700; over $19,050 to $77,400 for couples)
- 22% (over $38,700 to $82,500; over $77,400 to $165,000 for couples)
- 24% (over $82,500 to $157,500; over $165,000 to $315,000 for couples)
- 32% (over $157,500 to $200,000; over $315,000 to $400,000 for couples)
- 35% (over $200,000 to $400,000; over $400,000 to $600,000 for couples)
- 37% (over $500,000; over $600,000 for couples).

The new bill nearly doubles the standard deduction. For single filers, the bill increases the deduction to $12,000 from $6,350; for married couples filing jointly, it increases to $24,000 from $12,700. However, it eliminates personal exemptions. Previously, you were allowed to claim a $4,050 personal exemption for yourself, your spouse, and each of your dependents.

The bill preserves the state and local tax deduction for anyone who itemizes, but caps the amount that may be deducted at $10,000. Before, the deduction was unlimited for your state and local property taxes plus income or sales taxes.

The new tax law doubles the child tax credit. The new credit is $2,000 for children under age 17. The credit is also made available to higher earners by raising the income threshold under which filers may claim the full credit to $200,000 for single parents and $400,000 for married couples. These income thresholds stood at $75,000 and $150,000 respectively in previous years.

The new bill lowers the cap on mortgage interest deductions. If you take out a new mortgage on a first or second home, you will only be allowed to deduct the interest on debt up to $750,000, down from $1 million. Homeowners who already have a mortgage would be unaffected by the change.

The new tax law curbs who’s hit by the alternative minimum tax (AMT). The final bill keeps AMT, but reduces the number of filers subject to it by raising the income exemption levels to $70,300 for single filers, up from $54,300 previously; and $109,400 for married couples, up from $84,500.

One of the most significant changes is that the new law exempts almost everybody from the estate tax. While the bill does not call for a repeal of the estate tax, it essentially eliminates it by doubling the amount of money exempt from the estate tax to $10.98 million for individuals and $21.96 million for married couples.

The law does not change a taxpayer’s ability to deduct charitable contributions (assuming they itemize deductions). However, the increased standard deduction will reduce the number of taxpayers who itemize deductions and could impact future contributions.

Most Tier II deductions have been eliminated. These include fees paid to certified public accountants, financial advisers, and attorneys; an employee’s business expenses (tools, uniforms, supplies, travel, occupational licenses, etc.); investment expenses; home office deduction (some exceptions apply); and some education expenses.

529 accounts can now be used for K-12 education. Previously, these accounts could only be used for higher education. Up to $10,000 per year can be used on qualified K-12 education expenses.

To understand how these changes—as well as others not listed above—may impact you, contact your CPA.

**Q:** Under the new tax law, were any significant changes made to charitable gifting deductions?

**A:** There were no changes to the charitable gifting rules under the new law. Individuals can donate up to 30% of their adjusted gross income if they are giving non-cash gifts to charity.

**FINANCIAL TIPS**

- The new law lowers the cap on mortgage interest deductions. If you take out a new mortgage on a first or second home, you will only be allowed to deduct the interest on debt up to $750,000, down from $1 million.
- The final bill keeps the alternative minimum tax, but reduces the number of filers subject to it by raising the income exemption levels to $70,300 for single filers, up from $54,300 previously; and $109,400 for married couples, up from $84,500.
- There were no changes to the charitable gifting rules under the new law. Individuals can donate up to 30% of their adjusted gross income if they are giving non-cash gifts to charity.
Ease patients’ financial pain points through billing transparency

Providing accurate cost estimates, freedom of payment choices will help

PAUL HOFFMAN

Mr. Hoffman is vice president of product development at Experian Health. This article was originally published by Urology Times sister brand Medical Economics.

In 2017, Black Book’s “Revenue Cycle Management” report revealed that the average patient was expected to pay more than $6,200 a year for insurance deductibles and other out-of-pocket costs. That’s almost 30% higher than average consumer health care costs in 2015. It’s also a harbinger of the shift toward consumerism that the health care industry needs to embrace.

The report also noted that 82% of providers and 92% of hospitals struggled with traditional collection methods. Millions of dollars in uncollected medical bills were left on the table. Rather than spending millions more paying third-party agencies to chase those payments, providers are closing the gap by changing their methods to cater to consumers.

That means more than providing excellent health care and service—it also means making everything, including admissions, billing, and coding, more transparent and convenient. When patients understand their out-of-pocket costs and the bills they receive are exactly what they expected, they’re more likely to pay them consistently and on time.

They’re also more likely to share their positive experiences online, which is the surest way for organizations to stand out from competitors. About 80% of Internet users in a study by Pew Research Center’s Internet and American Life Project said they search for health information online. Among that group, 21% said they looked up reviews about particular doctors and hospitals before making a choice.

Appealing to consumers has traditionally been more of a retail strategy. Stores need consumers to choose them. In health care, patients’ choices have been restricted by limitations in their insurance, Medicare, or Medicaid coverage, which means organizations have had a largely predetermined supply of patients.

As more costs for care and treatment shift to patients, they’re becoming more discerning about where they go to receive care. That is new territory for health care providers, which aren’t used to having to compete for business by appealing to savvy consumers.

Without the experience of retail marketing, hospitals and providers have found it difficult to attract and keep patients within the new health care economy. In an Experian Health consumer study, researchers found that the most significant pain points for patients lie in the financial aspects of their care.

When patients understand their out-of-pocket costs and the bills they receive are exactly what they expected, they’re more likely to pay them consistently and on time.

To create the type of experiences your patients will enjoy and tell the world about, you’ll need to address these pain points in a way that puts their needs first. Here are three pain points health care providers should address:

Patients receive inaccurate estimates about the cost of care. Health care billing is complicated by nature, especially as insurance policies, medical suppliers, and partnering organizations constantly evolve. It’s easier for hospitals to speculate what a patient might have to pay than to break down exactly what will factor into those costs. But it’s extremely frustrating for patients to receive bills much higher than they expected.

The discrepancy between the bill and the expectation leads to sinking customer satisfaction and more unpaid bills. Health care providers need to set more accurate expectations by taking the time to provide transparent price estimates, including how much the patient’s insurance company will cover and how much the patient will pay.

Patients are unable to compare prices among providers. As organizations make pricing easier to understand, patients will use this information to compare the treatment prices of local hospitals and providers. Organizations will need to keep their consumer-centric focus to stay relevant. If you ignore transparency or if the costs you project are difficult to understand, you could be left out of the comparison altogether.

Instead, make those comparisons a part of the conversation. If a trusted clinic offers MRIs for thousands of dollars less, work with the patient to ensure the imaging is high-quality enough instead of slamming the idea. Focusing on patients as consumers means taking every aspect of their well-being into account, including what’s financially best for them.

Patients are not allowed to make payment choices. Having the freedom to choose and the information necessary to do so wisely notably enhances patient satisfaction. It also makes it easier for patients to understand their bills from the very beginning, which is critical in appealing to their needs as consumers. No matter how high-quality their care was, patients still report negative experiences if they’re frustrated about their bills.

Being transparent helps clarify the bill, and patient-facing technologies, such as online patient portals, make it more convenient for them to pay. There’s no confusion about where to send the payments, and billing through a portal can be consolidated into a single payment or payment plan that patients can access almost anywhere.

Online portals can also incorporate credit data into the patient billing process. Credit data offers insight into each patient’s propensity to pay and financial disposition. This information allows organizations to identify the best financial pathway (payment plans, assistance, deposits, etc.) for the patient at the time of service—or even before.

Patient self-service products anticipate how to best help each patient by creating a proactive and compassionate mobile-first experience that empowers people to apply for financial assistance, activate payment plans, review insurance benefits, and estimate the cost of care.

Now that consumers are paying more for their health care out of their own pockets, they’re not willing to accept pain points from health care providers. Stand apart by being exactly what patients expect: an organization that caters to them as though their business matters.
SUTENT® (sunitinib maleate) SIGNIFICANTLY EXTENDED DISEASE-FREE SURVIVAL (DFS) VS PLACEBO

1.2-YEAR INCREASE IN MEDIAN DFS VS PLACEBO

DFS IN THE OVERALL STUDY POPULATION BASED ON BLINDED INDEPENDENT CENTRAL REVIEW

- DFS events occurred in 113 (36.6%) and 144 (47.1%) patients receiving SUTENT and placebo, respectively.
- The 5-year DFS rate was 59.3% and 51.3% for patients receiving SUTENT and placebo, respectively.
- This translates to an 8% absolute risk reduction in disease recurrence or death vs placebo at 5 years.
- For overall survival (OS), which was a secondary endpoint, data were not mature at the time of data cutoff, with 141/615 (23%) patient deaths.

INDICATION

SUTENT® (sunitinib maleate) is indicated for the adjuvant treatment of adult patients at high risk of recurrent renal cell carcinoma (RCC) following nephrectomy.

IMPORTANT SAFETY INFORMATION

Boxed Warning/Hepatotoxicity: Hepatotoxicity has been observed in clinical trials and postmarketing experience. Hepatotoxicity may be severe, and in some cases fatal. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended. Fatal liver failure has been observed. Monitor liver function tests before initiation of treatment, during each cycle of treatment, and as clinically indicated. Discontinue SUTENT for Grade 3 or 4 drug-related hepatic adverse reactions and discontinue if there is no resolution. Do not restart SUTENT if patients subsequently experience severe changes in liver function test results or have signs and symptoms of liver failure.

Cardiovascular events, including myocardial ischemia, myocardial infarction, left ventricular ejection fraction declines to below the lower limit of normal, and cardiac failure, including death, have occurred. Monitor patients for signs and symptoms of congestive heart failure. Discontinue SUTENT for clinical manifestations of congestive heart failure. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered. Baseline and periodic evaluations of left ventricular ejection fraction should also be considered while these patients are receiving SUTENT.

Hypertension may occur. Monitor blood pressure and treat as needed with standard antihypertensive therapy. In cases of severe hypertension, temporary suspension of SUTENT is recommended until hypertension is controlled.

Hemorrhagic events, including tumor-related hemorrhage, and viscus perforation (both with fatal events) have occurred. These events may occur suddenly, and in the case of pulmonary tumors may present as severe and life-threatening hemoptysis or pulmonary hemorrhage. Perform serial complete blood counts (CBCs) and physical examinations.

Cases of tumor lysis syndrome (TLS) (some fatal) have been reported. Patients generally at risk of TLS are those with high tumor burden prior to treatment. Monitor these patients closely and treat as clinically indicated. Discontinue SUTENT in patients developing TLS. Reversal of the effects of TLS has been observed after treatment was discontinued.

Proteinuria and nephrotic syndrome have been reported. Some of these cases have resulted in renal failure and fatal outcomes. Monitor patients for the development or worsening of proteinuria. Perform baseline and periodic urinalysis during treatment, with follow-up measurement of 24-hour urine protein as clinically indicated. Discontinue SUTENT treatment if a diagnosis of TLS is suspected, treatment must not be restarted.

Necrotizing fasciitis, including fatal cases, has been reported, including of the perineum and secondary to fistula formation. Discontinue SUTENT in patients who develop necrotizing fasciitis.

Thyroid dysfunction may occur. Monitor thyroid function in patients with signs and symptoms suggestive of thyroid dysfunction, including hyperthyroidism, hypothyroidism, and thyroiditis, and treat per standard medical practice.

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In a randomized, double-blind, placebo-controlled, phase 3 trial of patients at high risk of recurrent RCC following nephrectomy (N=615)

SUTENT® (sunitinib maleate) SIGNIFICANTLY EXTENDED DISEASE-FREE SURVIVAL (DFS) VS PLACEBO

1.2-YEAR INCREASE IN MEDIAN DFS VS PLACEBO

DFS IN THE OVERALL STUDY POPULATION BASED ON BLINDED INDEPENDENT CENTRAL REVIEW

- DFS events occurred in 113 (36.6%) and 144 (47.1%) patients receiving SUTENT and placebo, respectively.
- The 5-year DFS rate was 59.3% and 51.3% for patients receiving SUTENT and placebo, respectively.
- This translates to an 8% absolute risk reduction in disease recurrence or death vs placebo at 5 years.
- For overall survival (OS), which was a secondary endpoint, data were not mature at the time of data cutoff, with 141/615 (23%) patient deaths.
MOST COMMON ADVERSE REACTIONS (ARs)

- The most common ARs reported in ≥20% of patients receiving SUTENT for adjuvant treatment of RCC and more commonly than in patients given placebo (all grades, vs placebo) were mucositis/stomatitis (61% vs 15%), diarrhea (57% vs 22%), fatigue/asthenia (57% vs 34%), hand-foot syndrome (50% vs 10%), hypertension (39% vs 14%), altered taste (38% vs 6%), nausea (34% vs 15%), dyspepsia (27% vs 7%), abdominal pain (25% vs 9%), hypothyroidism/TSH increased (24% vs 4%), rash (24% vs 12%), bleeding events, all sites (24% vs 5%), and hair color changes (22% vs 2%).

STUDY DESIGN

- A multicenter, international, randomized, double-blind, placebo-controlled, phase 3 trial in patients at high risk of recurrent RCC following nephrectomy.
- Patients were required to have clear-cell histology and high risk of recurrence (defined as ≥T3 and/or N+ tumors).
- 615 patients were randomized 1:1 to receive either 50-mg SUTENT or placebo once daily on a schedule of 4 weeks on treatment followed by 2 weeks off:
  - Treatment was initiated 3-12 weeks postnephrectomy.
  - Unscheduled dose interruption and/or dose reduction to a minimum of 37.5 mg of SUTENT was allowed.
  - Treatment continued for 9 cycles (~1 year) or until disease recurrence, unacceptable toxicity, or withdrawal of consent.
- The primary endpoint of DFS was assessed by blinded independent central review (BICR).
- Secondary endpoints included OS and safety.

Hypoglycemia may occur. SUTENT can result in symptomatic hypoglycemia, which may lead to a loss of consciousness or require hospitalization. Reductions in blood glucose levels may be worse in patients with diabetes. Check blood glucose levels regularly during and after discontinuation of treatment with SUTENT. Assess if antidiabetic drug dosage needs to be adjusted to minimize the risk of hypoglycemia.

Osteonecrosis of the jaw (ONJ) has been reported. Consider preventive dentistry prior to treatment with SUTENT. If possible, avoid invasive dental procedures, particularly in patients receiving intravenous bisphosphonate therapy.

Impaired wound healing has occurred with SUTENT. Temporary interruption of therapy with SUTENT is recommended in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of therapy following major surgical intervention. Therefore, the decision to resume SUTENT therapy following a major surgical intervention should be based on clinical judgment of recovery from surgery.

Embryo-fetal toxicity and reproductive potential:
- Females: SUTENT can cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with SUTENT and for 7 weeks after the last dose.
- Males: Based on findings in animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment with SUTENT and for 7 weeks after the last dose.

Lactation: Because of the potential for serious adverse reactions in breastfed infants from SUTENT, advise a lactating woman not to breastfeed during treatment with SUTENT and for at least 4 weeks after the last dose.

Venous thromboembolic events: In patients treated with SUTENT (N=7527) for GIST, advanced RCC, pNET, and as adjuvant treatment for RCC, 3.5% of patients experienced a venous thromboembolic event, 2.2% were Grade 3-4.

Most common grade 3/4 ARs (adjuvant RCC): The most common grade 3/4 ARs reported in ≥5% of patients receiving SUTENT for adjuvant treatment of RCC and more commonly than in patients given placebo (vs placebo) were hand-foot syndrome (16% vs <1%), fatigue/asthenia (8% vs 2%), hypertension (8% vs 1%), and mucositis/stomatitis (6% vs 0%).

Most common grade 3/4 lab abnormalities (adjuvant RCC): The most common grade 3/4 lab abnormalities (occurring in ≥2% of patients receiving SUTENT) included neutropenia (13%), thrombocytopenia (5%), leukopenia (3%), lymphopenia (3%), elevated alanine aminotransferase (2%), elevated aspartate aminotransferase (2%), hyperglycemia (2%), and hyperkalemia (2%).


Please see Brief Summary of full Prescribing Information, including BOXED WARNING, on the following pages.
SUTENT® (sunitinib malate) capsules, for oral use

Brief Summary of Prescribing Information

**WARNING: HEPATOTOXICITY**

Hepatotoxicity has been observed in clinical trials and postmarketing experience. Hepatotoxicity may be severe, and in some cases fatal. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended.

**INDICATION AND USAGE**

SUTENT is indicated for the adjuvant treatment of adult patients at high risk of recurrent renal cell carcinoma (RCC) following nephrectomy.

**DOSAGE AND ADMINISTRATION**

**Recommended Dose**

The recommended dose of SUTENT for the adjuvant treatment of RCC is 50 mg taken orally once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2), for 9–6 cycles of treatment. SUTENT may be taken with or without food.

**Dosage Modification**

Dose interruption and/or dosage modification in 12.5 mg increments or decrements is recommended based on individual safety and tolerability. In the adjuvant RCC study, the minimum dose administered was 37.5 mg.

A dose reduction for SUTENT to a minimum of 37.5 mg daily should be considered if SUTENT must be coadministered with a strong CYP3A4 inhibitor.

A dose increase for SUTENT to a maximum of 87.5 mg daily should be considered if SUTENT must be coadministered with a CYP3A4 inducer. If dose is increased, the patient should be monitored carefully for toxicity.

**CONTRAINDICATIONS**

None.

**WARNINGS AND PRECAUTIONS**

**Hepatotoxicity.** SUTENT can cause severe hepatotoxicity, resulting in liver failure or death. Liver failure occurred at an incidence of <1% in clinical trials. Liver failure signs include jaundice, elevated transaminases and/or hyperbilirubinemia in conjunction with encephalopathy, coagulopathy, and/or renal failure. Liver function test abnormalities may increase in patients without clinical evidence of CHF who have an ejection fraction of ≥40% but <50% below baseline or the lower limit of normal if baseline ejection fraction is not obtained.

In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered. Carefully monitor patients for clinical signs and symptoms of CHF while receiving SUTENT. Baseline cardiac conditions and reductions of left ventricular ejection fraction (LVEF) should also be considered while these patients are receiving SUTENT.

Cardiovascular Events. Discontinue SUTENT in the presence of clinical manifestations of congestive heart failure (CHF) and/or and reduce the dose in patients without clinical evidence of CHF who have an ejection fraction of ≥40% but <50% below baseline or the lower limit of normal if baseline ejection fraction is not obtained.

In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered. Carefully monitor patients for clinical signs and symptoms of CHF while receiving SUTENT. Baseline cardiac conditions and reductions of left ventricular ejection fraction (LVEF) should also be considered while these patients are receiving SUTENT.

Cardiovascular events, including heart failure, cardiomyopathy, myocardial ischemia, and myocardial infarction, some of which were fatal, have been reported. In patients treated with SUTENT (N=7527) for adjuvant treatment of RCC and pNET, 3% of patients experienced heart failure; 71% of the patients with heart failure were reported as recovered. Fatal cardiac failure was reported in <1% of patients.

In the adjuvant treatment of RCC study, 11 patients in each arm experienced a decreased ejection fraction meeting Grade 2 CTCAE criteria (LVEF 40.0–50.0% and a 10–19% decrease from baseline). No patients had a Grade 3–4 decrease in ejection fraction. The ejection fractions of three patients in the SUTENT arm and 2 patients in the placebo arm did not return to ≥50% or baseline by the time of the last measurement. No patients who received SUTENT were diagnosed with CHF.

Patients who presented with cardiac events within 12 months prior to SUTENT administration, such as myocardial infarction, atrial fibrillation, unstable angina, or myocardial ischemic event, were monitored for evidence of left ventricular ejection fraction (LVEF) should also be considered while these patients are receiving SUTENT.

QT Interval Prolongation and Torsade de Pointes. SUTENT can cause QT interval prolongation in a dose-related manner and lead to an increased risk for ventricular arrhythmias including QT prolongation, symptomatic CHF, cerebrovascular accident or transient ischemic attack, or pulmonary embolism were excluded from SUTENT clinical studies. It is unknown whether patients with these concomitant conditions may be at a higher risk of developing drug-related left ventricular dysfunction.

**Osteonecrosis of the Jaw (ONJ).** ONJ has been observed in clinical trials and has been reported in postmarketing experience in patients treated with SUTENT. Concomitant exposure to other factors, such as bisphosphonates or dental disease, may increase the risk of osteonecrosis of the jaw. Consider preventive dental care prior to treatment with SUTENT. If possible, avoid invasive dental procedures while on SUTENT treatment, particularly in patients receiving concurrent bisphosphonate therapy.

**Hypoglycemia.** SUTENT can result in symptomatic hypoglycemia, which may lead to loss of consciousness or require hospitalization. Severe hypoglycemia has occurred in up to 19% of the patients treated with SUTENT for advanced RCC and GIST and in approximately 10% of the patients treated with SUTENT for pNET. In the adjuvant treatment of RCC study, no patients on SUTENT experienced hypoglycemia. For patients being treated with SUTENT for pNET, pre-existing abnormalities in glucose homeostasis were not present in all patients who experienced hypoglycemia. Reductions in blood glucose levels may be worse in diabetic patients. Check blood glucose levels regularly during and after discontinuation of treatment with SUTENT. Assess if anti diabetic drug dosage needs to be adjusted to maintain safe blood glucose levels.

**Thyroid Dysfunction.** Baseline laboratory measurement of thyroid function is recommended for toxicity. If thyroid dysfunction is detected, SUTENT treatment must not be restarted.

**Hypertension.** Baseline and periodic monitoring of the blood pressure is recommended. Carefully monitor patients for clinical signs and symptoms of HF while receiving SUTENT. Baseline cardiac conditions and reductions of left ventricular ejection fraction (LVEF) should also be considered while these patients are receiving SUTENT.

**Thrombotic Microangiopathy.** Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome, sometimes leading to renal failure or a fatal outcome, occurred in clinical trials and in postmarketing experience of SUTENT as monotherapy and in combination in combination with bevacizumab. Discontinue SUTENT in patients developing TMA. Reversal of the effects of TMA has been observed after treatment was discontinued.

**Proteinuria.** Proteinuria and nephrotic syndrome have been reported. Some of these cases have resulted in renal failure and fatal outcomes. Monitor patients for the development or worsening of proteinuria, including baseline and during treatment for 24-hour urine protein as clinically indicated. Interrupt SUTENT and dose reduce for 24-hour urine protein ≥3 gms. Discontinue SUTENT for patients with nephrotic syndrome or repeat episodes of urine protein ≥3 gms despite dose reductions. The safety of continued SUTENT treatment in patients who must not be exposed to severe proteinuria has not been systematically evaluated.

**Thrombocytopenia.** Thrombocytopenia has been reported in <0.1% of SUTENT treated patients. Patients with thrombocytopenia (~1%) out of 304 patients in the placebo arm had dose reductions.

**Tumor Lysis Syndrome (TLS).** Cases of TLS, some fatal, occurred in clinical trials and have been reported in postmarketing experience, primarily in patients with RCC or GIST treated with SUTENT. Patients generally at risk of TLS are those with high tumor burden prior to treatment. Monitor these patients closely and treat as clinically indicated.

**Serious, sometimes fatal, gastrointestinal complications including gastrointestinal perforation, have been reported in patients with intra-abdominal malignancies treated with SUTENT.**

**Tumor Lysis Syndrome (TLS).** Cases of TLS, some fatal, occurred in clinical trials and have been reported in postmarketing experience, primarily in patients with RCC or GIST treated with SUTENT. Patients generally at risk of TLS are those with high tumor burden prior to treatment. Monitor these patients closely and treat as clinically indicated.

**Thrombocytopenia.** Thrombocytopenia has been reported in <0.1% of SUTENT treated patients. Patients with thrombocytopenia (~1%) out of 304 patients in the placebo arm had dose reductions.
Infections and infestations: serious infection (with or without neutropenia). The infections most commonly observed with SUTENT treatment include respiratory, urinary tract, skin infections, and septicemic shock.

Capillary/vascular leak syndrome: fatal outcome, sometimes associated with tumor necrosis and/or regression; myopathy and/or rhabdomyolysis with or without acute renal failure. Patients with signs or symptoms of muscle toxicity should be managed as per standard medical practice.

Respiratory disorders: pulmonary embolism.

Skin and subcutaneous tissue disorders: pyoderma gangrenosum, including positive dechallenge.

Vascular disorders: arterial thromboembolic events. The most frequent events included cerebrovascular accident, transient ischemic attack, and cerebral infarction.

*including some fatalities.

**Drug interactions**

**CYP3A4 Inhibitors.** Strong CYP3A4 inhibitors such as ketoconazole may increase sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. Concurrent administration of SUTENT with the strong CYP3A4 inhibitor, rifampin, resulted in a 22% and 46% reduction in the combined (sunitinib + primary active metabolite) C_{max} and AUC_{0-∞} values, respectively, after a single dose of SUTENT in healthy volunteers. Coadministration of SUTENT with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, azithromycin, indinavir, nevirapine, ritonavir, saquinavir, telithromycin, voriconazole) may increase sunitinib concentrations. Grapefruit may also increase plasma levels of sunitinib. A dose reduction for SUTENT should be considered when it must be coadministered with strong CYP3A4 inhibitors (see Dosage and Administration).

**CYP3A4 Inducers.** CYP3A4 inducers such as rifampin may decrease sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. Concurrent administration of SUTENT with the CYP3A4 inducer, rifampin, resulted in a 23% and 46% reduction in the combined (sunitinib + primary active metabolite) C_{max} and AUC_{0-∞} values, respectively, after a single dose of SUTENT in healthy volunteers. Coadministration of SUTENT with inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, St. John’s Wort) may decrease sunitinib concentrations. St. John’s Wort may decrease sunitinib plasma concentrations unpredictably. Patients receiving SUTENT should not take St. John’s Wort concurrently. A dose increase for SUTENT should be considered when it must be coadministered with CYP3A4 inducers (see Dosage and Administration).

**In Vitro Studies of CYP Inhibition and Induction.** In vitro studies indicated that sunitinib does not induce or inhibit major CYP enzymes. The in vitro studies in human liver microsomes and hepatocytes of the activity of CYP isomers CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP4B1 indicated that sunitinib and its primary active metabolite are unlikely to have any clinically relevant drug-drug interactions with drugs that may be metabolized by these enzymes.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary.** Based on animal reproduction studies and its mechanism of action, SUTENT can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform a drug-associated risk. In animal developmental and reproductive toxicology studies, oral administration of sunitinib to pregnant rats and rabbits throughout organogenesis resulted in teratogenicity (embryolethality, craniofacial and skeletal malformations) at 5.0 and 0.5 times the recommended daily doses (RDD), respectively (see Data). Advise pregnant women or females of reproductive potential of the potential hazard to a fetus.

The background risk of major birth defects and miscarriage for the indicated populations are unknown. However, the estimated background risk in the United States (U.S.) general population of major birth defects is 2% - 4% and of miscarriage is 15% - 20% of clinically recognized pregnancies.

**Data.**

**Animal Data.** In a female fertility and early embryonic development study, female rats were administered oral sunitinib (0.5, 1.5, 5 mg/kg/day) for 21 days prior to mating and for 7 days after mating. Embryolethality was observed at 5 mg/kg/day (approximately 5 times the AUC in patients administered the RDD of 50 mg/day).

In embryo-fetal developmental toxicity studies, oral sunitinib was administered to pregnant rats (0.3, 1.5, 5, 5 mg/kg/day) and rabbits (0.5, 1.5, 5, 50 mg/kg/day) during the period of organogenesis. In rats, embryolethality and skeletal malformations of the ribs and vertebrae were observed at the dose of 5 mg/kg/day (approximately 5.5 times the systemic exposure [combined AUC of sunitinib + primary active metabolite] in patients administered the RDD). No adverse fetal effects were observed in rats at doses ≤3 mg/kg/day (approximately 2 times the AUC in patients administered the RDD). In rabbits, embryolethality was observed at 5 mg/kg/day (approximately 3 times the AUC in patients administered the RDD), and craniofacial malformations (clipped tip and clipped palate) were observed at 3 mg/kg/day (approximately 0.3 times the AUC in patients administered the RDD of 50 mg/day).

Sunitinib (0.3, 1.3 mg/kg/day) was evaluated in a pre- and postnatal development study in pregnant rats. Maternal body weight gains were reduced during gestation and lactation at doses ≥1 mg/kg/day (approximately 5 times the AUC in patients administered the RDD). At 3 mg/kg/day (approximately 2 times the AUC in patients administered the RDD), reduced neonate body weights were observed at birth and persisted in the offspring of both sexes during the preweaning period and in males during postweaning period. No adverse developmental effects were observed at doses ≤1 mg/kg/day.

**Lactation.** There is no information regarding the presence of sunitinib and its metabolites in human milk. Sunitinib and its metabolites were excreted in rat milk at concentrations up to 12-fold higher than in plasma. Because of the potential for serious adverse reactions in breastfed infants from SUTENT, advise a lactating woman not to breastfeed during treatment with SUTENT and for at least 4 weeks after the last dose.

**Data.**

**Animal Data.** In lactating female rats administered 15 mg/kg, sunitinib and its metabolites were excreted in milk at concentrations up to 12-fold higher than in plasma.

**Females and Males of Reproductive Potential.** Based on animal reproduction studies and its mechanism of action, SUTENT can cause fetal harm when administered to a pregnant woman.

**Pregnancy Testing.** Females of reproductive potential should have a pregnancy test before treatment with SUTENT is started.
Contraception

Females. Advise females of reproductive potential to use effective contraception during treatment with SUTENT for at least 4 weeks after the last dose.

Males. Based on findings in animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment with SUTENT and for 7 weeks after the last dose.

Infertility

Based on findings in animals, male and female fertility may be compromised by treatment with SUTENT.

Pediatric Use

The safety and efficacy of SUTENT in pediatric patients have not been established.

Physeal dysplasia was observed in cynomolgus monkeys with open growth plates treated for ≥3 months (3 month dosing, 6, 12 mg/kg/day; 8 cycles of dosing 0.3, 1.5, 6.0 mg/kg/day) with sunitinib at doses that were ≥4.8 times the RDD based on systemic exposure (AUC). In developing rats treated continuously for 3 months (1.5, 5.0, and 15.0 mg/kg) or 5 cycles (0.3, 1.5, and 6.0 mg/kg/day), bone abnormalities consisted of thickening of the epiphyseal cartilage of the femur and an increase in fracture of the tibia at doses ≥5 mg/kg (approximately 10 times the RDD based on AUC). Additionally, cartilage of the teeth were observed in rats at ≥5 mg/kg. The incidence and severity of physeal dysplasia were dose related and were reversible upon cessation of treatment; however, findings in the teeth were not. A no-effect level was not observed in monkeys treated continuously for 3 months, but was 1.5 mg/kg/day when treated intermittently for 8 cycles. In rats the no-effect level in bones was ≤0.2 mg/kg/day.

Geriatric Use

Among the 158 patients at least age 65 receiving adjuvant SUTENT/placebo for RCC, the hazard ratio for disease-free survival was 0.59 (95% CI: 0.36, 0.95). Among patients 65 years and older receiving adjuvant SUTENT/placebo for RCC, 50% patients (9% in the SUTENT arm experienced a Grade 3–4 adverse reaction, compared to 15 patients (9%) in the placebo arm.

Hepatic Impairment

No dose adjustment to the starting dose is required when administering SUTENT to patients with Child-Pugh Class A or B hepatic impairment. Sunitinib and its primary metabolite are primarily metabolized by the liver. Systemic exposures after a single dose of SUTENT were similar in patients with mild or moderate (Child-Pugh Class A) and severe (Child-Pugh Class C) hepatic impairment compared to patients with normal hepatic function. SUTENT was not studied in patients with severe (Child-Pugh Class C) hepatic impairment. Studies in cancer patients have excluded patients with ALT >2.5 × ULN or, if due to liver metastases, >5.0 × ULN.

Renal Impairment

No adjustment to the starting dose is required when administering SUTENT to patients with mild (CLcr 50–80 mL/min), moderate (CLcr 30–50 mL/min), or severe (CLcr <30 mL/min) renal impairment who are not on dialysis. In patients with end-stage renal disease (ESRD) on hemodialysis, no adjustment to the starting dose is required. However, compared to patients with normal renal function, the sunitinib exposure is 47% lower in patients with ESRD on hemodialysis. Therefore, the subsequent doses may be increased gradually up to 2-fold based on safety and tolerability.

OVERDOSAGE

Treatment of overdose with SUTENT should consist of general supportive measures. There is no specific antidote available for the treatment of SUTENT overdosage. If ingestion of an unabsorbed drug should be achieved by emesis or gastric lavage. Cases of accidental overdose have been reported; these cases were associated with adverse reactions consistent with the known safety profile of SUTENT, without adverse reactions. A case of intentional overdose involving the ingestion of 1500 mg of SUTENT in an attempted suicide was reported without adverse reaction. In nonclinical studies, mortality was observed following as few as 5 daily doses of 500 mg/kg (3000 mg/m²) in rats. At this dose, signs of toxicity included impaired muscle coordination, head shakes, hypoactivity, ocular discharge, piloeruption, and gastrointestinal distress. Mortality and similar signs of toxicity were observed at lower doses when administered for longer durations.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of sunitinib has been evaluated in 2 species: rasH2 transgenic mice and Sprague-Dawley rats. There were similar dose-related, increased incidences of unpaired drug showing signs of toxicity included impaired muscle coordination, head shakes, hypoactivity, ocular discharge, piloeruption, and gastrointestinal distress. Mortality and similar signs of toxicity were observed at lower doses when administered for longer durations.

In developing rats treated intermittently for 8 cycles. In rats the no-effect level in bones was ≤0.2 mg/kg/day.

Gastrointestinal Effects and Toxicities

Advise patients that diarrhea, nausea, vomiting, and constipation may develop during SUTENT treatment and to seek immediate medical attention if they experience persistent or severe abdominal pain because cases of gastrointestinal perforation and fistulae have been reported in patients taking SUTENT.

Dermatologic Effects and Toxicities

Advise patients that depigmentation of the hair or skin may occur during treatment with SUTENT due to the drug color (yellow). Other possible dermatologic effects may include dryness, thickness or cracking of skin, blister or rash on the palms of the hands and soles of the feet. Severe dermatologic toxicities including Stevens-Johnson syndrome, Toxic Epidermal Necrolysis, erythema multiforme, and necrotizing fasciitis have been reported. Advise patients to immediately inform their healthcare provider if severe dermatologic reactions occur.

Hyperglycemia

Advise patients that SUTENT can cause severe hyperglycemia and may be more severe in patients with diabetes taking antidiabetic medications. Inform patients of the signs, symptoms, and risks associated with hyperglycemia. Advise patients to immediately inform their healthcare provider if severe signs or symptoms of hyperglycemia occur.

Osteonecrosis of the Jaw

Advise patients that SUTENT can cause osteonecrosis of the jaw and to contact their healthcare provider if they experience signs or symptoms of hyperglycermia.

Cardiovascular Events

Advise patients to contact their healthcare provider if they develop symptoms of heart failure.

QT Prolongation and Torsade de Pointes

Inform patients of the signs and symptoms of QT prolongation. Advise patients to contact their healthcare provider immediately in the event of syncpe, pre-syncopal symptoms, and cardiac palpitations.

Hypertension

Advise patients of the signs and symptoms of hypertension. Advise patients to undergo blood pressure monitoring and to contact their healthcare provider if blood pressure is elevated or if they experience signs or symptoms of hypertension.

Hemorrhagic Events

Advise patients that SUTENT can cause severe bleeding. Advise patients to immediately contact their healthcare provider for bleeding or symptoms of bleeding.

Gastrointestinal Disorders

Advise patients that gastrointestinal disorders such as diarrhea, nausea, vomiting, and constipation may develop during SUTENT treatment and to seek immediate medical attention if they experience persistent or severe abdominal pain because cases of gastrointestinal perforation and fistulae have been reported in patients taking SUTENT.

Concomitant Medications

Advise patients to inform their healthcare providers of all concomitant medications, including over-the-counter medications and dietary supplements.

Embryo-Fetal Toxicity

Advise females to inform their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy.

Embryo-Fetal Toxicity

Advise females of reproductive potential to use effective contraception during treatment and for 4 weeks after receiving the last dose of SUTENT.

Advise males with female partners of reproductive potential to use effective contraception during treatment and for 7 weeks after receiving the last dose of SUTENT.

Lactation

Advise lactating women not to breastfeed during treatment with SUTENT and for at least 4 weeks after the last dose.

Infertility

Advise patients that male and female fertility may be compromised by treatment with SUTENT.

Missed Dose

Advise patients that miss a dose of SUTENT by less than 12 hours to take the missed dose right away. Advise patients that miss a dose of SUTENT by more than 12 hours to take the next scheduled dose at its regular time. This product’s label may have been updated. For full prescribing information, please visit www.pfizer.com.

Rx only

Revised: April 2018
Telemedicine policies advance with technology

State, federal initiatives starting to address regulatory hurdles

The prospect of delivering patient-centered care via telemedicine is invigorating for many urologists, particularly in light of nationwide workforce shortages. Integration of this technology into daily practice has been largely stymied, however, by confused licensing standards and restrictive reimbursement policies. State lawmakers and federal regulators have taken significant steps in recent months to address these constraining conditions.

The United States will face an overall shortage of more than 100,000 physicians by 2030, and more than half of that number will come from specialty physicians, according to the Association of American Medical Colleges, which reports “the supply of surgeons is projected to have little growth by 2030, but projected demand is expected to increase, resulting in a shortage of between 19,800 and 29,000 surgeons by 2030.”

According to the Center for Connected Health Policy, 39 states and the District of Columbia have laws that govern private payer reimbursement of telehealth.

According to the Center for Connected Health Policy, 39 states and the District of Columbia have laws that govern private payer reimbursement of telehealth.

Urology has seen a greater than 10% decline in the number of specialists per capita over the past 20 years, and with more than 44% of urologists aged 55 or older, that drop will grow with retirements unless Congress lifts the cap on Medicare-funded residency positions imposed in 1997. The number of urologists who practice in rural areas is falling, as well. According to the 2016 AUA Census, “Less than 10 percent of practicing urologists in the United States maintain their primary practice locations in non-metropolitan areas.”

Defining telehealth

Telehealth, according to the Centers for Medicare & Medicaid Services, is “the provision of clinical services to patients by physicians and practitioners from a distance via electronic communications.” Non-simultaneous telemedicine involves after-the-fact interpretation or assessment, such as teleradiology services, while simultaneous telemedicine includes real-time interpretation or assessment, such as electronic ICU services, psychiatry, or dermatology.

Urologist Lisa Finkelstein, DO, has become a leading authority on telehealth. As president of the Wyoming Medical Society, Dr. Finkelstein was the lead witness appearing (via HIPAA-compliant Zoom video conferencing) before a legislative committee in November 2018. She also shares her experience as a member of the AACU State Advocacy Network.

“Here in rural Wyoming, 2019 has been one of the snowiest winters on record,” Dr. Finkelstein reported. “Passes and canyons have been closed for days at a time. I say, ‘Let it Snow and Tele-On!’ As barriers to telemedicine are removed, our patients would not have to cancel their appointments. Instead, they just sign into their Zoom account and see their urologist, cardiologist, or primary care doctor. The ideas are endless.”

Laws that authorize telehealth from a cross-state licensing standpoint are widespread, but policies that govern reimbursement and liability are inconsistent (at best). The Interstate Medical Licensure Compact facilitates physician licensing across state lines. The compact was finalized in 2014, and by 2017, the requisite number of states adopted it to allow the framework to be effective.

In January 2019, Michigan became the 25th state to join. According to the Federation of State Medical Boards, to date, 4,511 licenses have been issued and 2,400 applications processed by a commission that administers these activities.

According to the Center for Connected Health Policy, 39 states and the District of Columbia have laws that govern private payer reimbursement of telehealth. This is an increase of one state (Kansas) since spring 2018. Some laws require reimbursement to be equal to in-person coverage, but most only require parity in covered services, not reimbursement amount. Washington State Senator Randi Becker, a past AACU Distinguished Leadership Award honoree, introduced several bills addressing telemedicine this year, including a proposal to ensure that health plans reimburse telemedicine at the same rate as services provided in office.

On the liability front, much depends on one’s insurer. On a case-by-case basis, policies may cover a provider’s activities that extend into another state. However, due to various reasons such as a lack of a cap on damages, many carriers may not be willing to provide coverage across state lines. Whatever the case, providers are advised to assume they will be subject to the laws of another state on issues such as professional standards and standard of care, informed consent, statute of limitations, pre-litigation screening, evidentiary rules, and expert witness qualifications.

Medicare reimbursement key

For urologists, integration of telemedicine into one’s practice will rely heavily on Medicare reimbursement of those services. The 2019 Medicare payment rule, for the first time, includes payment for technology-based services like brief check-ins and virtual consultations. In a November 2018 speech, CMS Administrator Seema Verma said, “…many times a virtual check-in will resolve patient concerns in a convenient manner that gets them the care they need, and avoids unnecessary costs for the system.”

Verma added that Medicare “will also be paying for virtual consultations between physicians, and evaluation of remote pre-recorded images and video. For example, a patient could now text a picture of a mole on their skin to a dermatologist for examination.”

In another proposal issued in late 2018, CMS solicited comments on whether to allow Medicare Advantage plans to offer additional telehealth benefits in plan year 2020.

AACU President Mark Edney, MD, MBA, asserted, “In no time, caring for patients via telemedicine will happen on a daily basis. The AACU is committed to representing practicing urologists as the laws, regulations, and payer policies that govern these services are hammered out.”
Urologic trauma/reconstruction: What the future holds

The 2016 AUA clinical guideline for male urethral stricture reflects evolving management strategies for this condition, and the number of urologists specializing in reconstruction is on the rise. In this interview, Richard Santucci, MD, discusses current trends in urologic trauma/reconstruction as well as the promise of penile transplantation.

Q: Let’s discuss urethral stricture. Traditionally, urethral dilation or direct vision internal urethrotomy (DVIU), whether done with a cold knife or laser, has been part of a urologist’s practice. How does the AUA clinical guideline for male stricture suggest a change in this practice?

A: I think the data was finally available to see that DVIU or a dilation is almost never a lasting cure. DVIU or dilation is a very efficient surgery if the person cannot urinate and you can dilate them, pass a catheter, and they can now pass urine, but as part of a long-term repertoire, it definitely does not cure the patient.

The data reflecting that was then analyzed by the AUA Practice Guidelines Committee, which created a guideline that said, if you want to use DVIU or dilation for a stricture once, that’s probably OK. But you shouldn’t do it a second time or at least should offer the patient curative urethroplasty because the chance of success with DVIU or dilation is incredibly low.

Those suggestions become even more strident if the stricture is particularly long. In that case, you might not even bother with one DVIU or dilation because it will absolutely fail. This also applies when the stricture is any length in the penile urethra; those just don’t seem to respond in a lasting fashion to DVIU or dilation.

Q: There are few urethroplasty surgeons in the U.S. What is the state of male reconstructive training?

A: This is a problem. We’ve now got a guideline that maybe our infrastructure cannot support. When I came out of a training program in 2000, there were two or three training programs in the United States. The good news is, there are now 20 training programs, and it’s much more common that an individual resident even outside of fellowship training will have some good experience in doing urethral strictures. Thank goodness there are more and more practitioners who can help with that. There are huge swathes of geographic areas in the United States that don’t have a single person who is interested in or able to do urethroplasty, and that may require referral to a center of excellence even with all the implications of how difficult that can be economically/socially, but that’s getting to be the standard.

Q: In the past, devices haven’t worked. I’ve spent my life working on one. Is there any future hope of different treatment approaches, such as tissue engineering?

A: There’s always hope. There’s something challenging about placing devices in areas with urine contact. For example, you know more than anyone that the UroLume was facing two problems. One is that it was in contact with urine, so the chance of getting stones and things like that was high, and two, it was trying to fight one of the most efficient processes in the entire body—scar formation. The device simply wasn’t up to the task of fighting this really elemental process and the troubles of urine precipitating on objects in contact.

The future of urethral surgery certainly involves an off-the-shelf component so that we don’t have to harvest tissue from the cheek, for example. That would be great. Is that coming tomorrow? Sure, it just depends on when your “tomorrow” is. Another possibility is working with people like Dr. Anthony Atala for something like taking a mucosal biopsy, seeding an acellular matrix with your own cells, and then placing your own urethral tissue back in.

Q: What are your views on penile transplant versus reconstruction?

A: Penile transplant is a fascinating area. Obviously, the recent penile transplant performed on a seriously injured soldier has captured the news. Interestingly, the very first penile transplant, which was done by Chinese surgeons, was removed for social reasons. It was successful technically but they didn’t discuss it with the patient thoroughly enough, he didn’t want it anymore, and it was removed.

The second and third successful penile transplants were done in South Africa, and the surgeons only announced it after 1 year of success.

It’s important to understand that the immune situation in skin is very different than that in solid organs. The first solid organ transplant was performed in 1959. The first face...
transplant was performed in the 1990s. Why the delay? Skin is highly immunogenic; the amount of immunosuppression you have to give patients knocks down the response in the skin to near-fatal levels, so it can be very difficult to run the immunosuppression on these patients.

**Q:** This is particularly vexing because of the trauma. I’m at the VA, and I’m seeing more veterans come back from war requiring phallic reconstruction. Current reconstructive techniques are not satisfying, tissue engineering reconstruction seems to be a ways off, and transplantation is therefore certainly very attractive.

**A:** Yes, it’s an issue, and what you’re describing is a clinical situation where we can see the edge of the cure but we don’t quite have the know how to move forward with phallic-genito reconstruction. Phalloplasty is a tried and true answer, but presents many, many problems.

Where do you see the genitourinary reconstructive surgeon playing a role in trauma?

**GOPAL H. BADLANI, MD**

I would certainly like to see every general urologist know how to handle the ABCs of trauma because they’re going to be called on to handle these issues in many cases.

**RICHARD SANTUCCI, MD**

I spent 18 years in the reconstructive urology space, and it could not have been more interesting and surgically fulfilling. Then out of the corner of my eye, I saw a whole “Mount Everest” of reconstructionists. It’s getting better in terms of the experience in Fournier’s gangrene and its sequelae.

**Q:** I think the general urologist perhaps sees more emergent scrotal infection cases, which require extensive debridement. Do you have any thoughts about or tips for a general urologist who might get called in and how to not minimize the concern?

**A:** There are some real surgical emergencies in urology, and scrotal infection is definitely one of the top three. Keeping Fournier’s gangrene or mixed necrotizing infection in your top three differential for every patient you see is a good idea because you really can’t (safely) miss it.

I also have seen some errors, perhaps even associated with medicolegal cases, where somebody says, “I don’t know if that is or isn’t Fournier’s gangrene.” They decide it isn’t, but it is.

I would argue that if you’re not sure, you probably need to do more. Consult with a colleague. Get a CT scan. That sounds silly, but the CT scan will often show gas that you can’t appreciate. I learned this as a fellow: Take the patient to the operating room and create a small incision. If you find beautiful, healthy tissue and you’re wrong, great. Most of the time, you won’t find that; you’ll find dead tissue.

I also find some serious under-debridement problems in which the debridement is done but somehow the practitioner without a lot of experience in Fournier’s feels they’ve gone far enough. But you’ve only gone far enough when all the dead tissue is gone. I would cut tissue with abandon and let the reconstructionist worry about how they’re going to piece it together later.

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**TRANSGENDER MEDICINE: THE UROLOGIST’S SCOPE**

**Q:** Please discuss your career path from reconstructive urology to transgender medicine.

**A:** I spent 18 years in the reconstructive urology space, and it could not have been more interesting and surgically fulfilling. Then out of the corner of my eye, I saw a whole “Mount Everest” of reconstructive urology problems—transgender surgery. My wife and I made the hard decision to switch careers, switch cities, and go down to Austin, TX. Most people don’t know that Austin is the home of one of the busiest transgender practices in the world. I was fortunate to fit into their hiring needs, they trained me up, and now I’m a full-time transgender surgeon.

**Q:** What is the scope of transgender issues in medicine, and how is the urologist involved?

**A:** Clinically, it’s quite a large issue. Many established surgeons have year-and-a-half waiting lists because there’s a huge backlog of untreated patients.

The urologist, as you can imagine, fits into a whole scenario of plastic surgeons and other practitioners. For a phalloplasty, which would be a female-to-male transition, there may be four surgeons operating. As the urologist, I would be doing the vaginectomy, a 10- to 14-cm urethral lengthening, vaginal closure, creation of a scrotum, and then hooking up the urethra to the skin urethra that makes up the phallic, which is actually constructed by a second plastic surgery team.

I also do male-to-female surgery—vaginoplasty—and that’s more like one surgeon with one assistant. It’s been very gratifying as a technical operation, and it’s been gratifying to work with the patients, who are highly motivated individuals.
PRIOR AUTH
continued from page 1

Christopher Bayne, MD

“I think if the insurance companies would just listen to what you’re saying and handle things on a case-by-case basis, they would see that we are reasonable and we are trying to provide the best for patients.”

To repairing cleft lip, which is often covered.

“I think if the insurance companies would just listen to what you’re saying and handle things on a case-by-case basis, they would see that we are reasonable and we are trying to provide the best for patients,” Dr. Bayne said.

Prior authorization’s toll

The American Medical Association recently reported on findings from a survey of 1,000 practicing physicians, including specialists, asking about their experiences with prior authorization. The online survey, sent out in December 2018, suggests prior authorization can be more than an administrative burden. It can harm patients.

More than nine in 10 doctors said prior authorization has a significant or somewhat negative impact on clinical outcomes. More than one-fourth (28%) said prior authorization has led to a serious adverse event such as a death, hospitalization, disability, or permanent bodily damage.

Three-fourths of physicians said prior authorization can lead to treatment abandonment, and 91% indicated it results in care delays.

Nearly 90% of those surveyed report prior authorization burdens have increased significantly or somewhat in the last 5 years, and 86% claim the burden associated with prior authorization is high or extremely high in their practices.

More than one in three physicians surveyed by the AMA have hired staff to work on prior authorizations.

The bleak picture in medicine overall is much the same in urology, according to Christopher M. Gonzalez, MD, MBA, chair of the AUAs Public Policy Council. The AUA surveyed members in 2016 and found prior authorization has profound impacts on the specialty.

“We found out urology offices were spending on average 14 hours a week on prior authorization. And it can be anywhere from one to three full-time equivalents that doctors’ offices have to hire to deal with this,” said Dr. Gonzalez, who is professor and chair of urology at Loyola Medicine and Loyola University Chicago Stritch School of Medicine, Maywood, IL.

The AUA survey found urologists were most likely to encounter the need for prior authorizations when prescribing medications, including those for overactive bladder, erectile dysfunction, cancer, and low testosterone. Prior authorizations are also common when urologists order CT or MRI scans or perform outpatient and inpatient surgery.

“The average time it takes a urology practice to make these calls is 19 to 20 minutes,” Dr. Gonzalez said. “So, we asked our doctors if this is a problem: 75% said the burden is high or extremely high for the practice, and 90% of our doctors said access to care is being delayed and patient care is being harmed.”

The denial rate in urology is about 24%, according to Dr. Gonzalez.

“So, three-fourths of the time, payers approve these things, but you have to jump through hoops,” he said.

The worst offender for prior authorization among insurers, according to the AUA survey, is Blue Cross Blue Shield, followed by United Healthcare and Aetna.

A 2019 study looked at what it costs physician practices to interact with health insurance plans, including for prior authorization. The authors estimated the cost to practices of interactions with plans is at least $23 to $31 billion annually (Health Aff [Millwood] 2009, 28:w333–43).

On its website, America’s Health Insurance Plans states: “Insurance providers use prior authorization under the supervision of medical professionals, promoting safe, timely, evidence-based, affordable and efficient care. Prior authorization requires advance approval of coverage for a medical service. It’s applied to less than 13 percent of treatments.”

The association did not respond to a request for an interview.

Hope at the state level

States are working on bills that could help providers and patients with burdens created by prior authorization. And for those states that need it, the AACU is there to help with its State Advocacy Network, according to Dr. Reha.

The AACU has a network in place to work with states to push forward urologist-supported legislation. That includes contact phone numbers and emails, information, and data, as well as the people power to lobby at the state capital, Dr. Reha.

Tips for easing prior authorization’s toll

There are steps practices can take to make prior authorization more efficient and less frustrating, according to Kenneth T. Hertz, principal at the Medical Group Management Association. Hertz’s tips:

Ducks in order. Make sure the people in the office charged with prior authorization are trained and knowledgeable. That should reduce follow-up phone calls.

Consider a cheat sheet. “From working with patients, you know which plans and which procedures or diagnostic tests or medications require prior authorization, so why not put together a cheat sheet? Put it on the practice’s intranet, so you can access it right from your computer,” Hertz said.

Prepare during the morning huddle. For practices that have a morning huddle, Hertz recommended planning for patients that will need prior authorization.

“If somebody has major hematuria, we may know that you’ll want to do a cystoscopy, so maybe you ought to have the paperwork ready to go,” Hertz said. “I think generally you can pretty much count on urodynamics and cystoscopy needing prior authorization.”

Consider technology. Some electronic solutions or software solutions can interface and integrate fully with an electronic health record. But for those solutions to be effective, practices should look for a solution provider that offers software that can reach in and grab information from an EHR and automatically populate a form.

“It also involves working with a company that has knowledge of what plans require prior authorizations, for what procedures, what medications, etc. and keeps that information updated and current. Some of those solutions will file prior authorization forms and follow up,” Hertz said. “That costs money but so does hiring staff to do prior authorization.”

Large practice? Use your clout. Larger practices that are parts of consortiums or are regionally affiliated with other urology practices can join and negotiate with payers.

“They kind of set up a standardized protocol, which mitigates the need for a direct prior authorization on every single patient,” Hertz said.

Play nice. “So many times we look at the payers as our enemies. While we may get into combative situations from time to time, if we can work collaboratively with them, particularly in a situation like prior authorization, it benefits everybody—most assuredly the patient,” Hertz said.
States are making progress, with a number of bills proposed (see, “Select state proposals at a glance,” right). The Commonwealth of Virginia, for example, has two bills that address prior authorization issues supported by both the AACU State Advocacy Network and the Medical Society of Virginia, according to Dr. Reha. In the Virginia Senate, SB 1607 includes several tenets pertaining to prior authorization, including the provision that “if a carrier has previously authorized an invasive or surgical health care service as medically necessary and during the procedure the health care provider discovers clinical evidence prompting the provider to perform a less or more extensive or complicated procedure than was previously authorized, then the carrier shall pay the claim, provided that it is appropriately coded consistent with the procedure actually performed.”

Another bill in Virginia, HB 2126, addresses step therapy reform by including a faster, more efficient exemptions process for patients who need treatments or are already on effective treatment, according to Dr. Reha. Step therapy is a process where prescribers have to try less expensive therapies before they can justify prescribing more expensive or newer therapies. An example of harm from step therapy in urology is in treatment of overactive bladder. “If you know somebody is going to respond to one of the newer generation overactive bladder agents or maybe they’ve been on it in the past and you know it’s going to work, the patient shouldn’t have to first fail something like oxybutynin chloride,” Dr. Reha said. “We’re not saying that everyone should go to the newer agents, but if there are medical reasons, there should be an exemptions policy.”

Both Virginia bills passed both the Senate and House unanimously and were awaiting the governor’s signature at press time. On a national level, the AUA is holding an annual insurance roundtable with commercial insurance agents, but if there are medical reasons, there should be an exemptions policy. A health plan that denies prior authorization for a prescription drug must provide a list of acceptable alternatives. Insurers must develop processes for electronic prior authorizations. Standardize and streamline the prior authorization process across all health insurers; any prior auth request shall be deemed granted if a final determination is not made within 5 business days. Shorten the time frame during which an insurer has to determine whether a preauthorization request is medically necessary from 3 business days to 3 days. All payers must develop standardized prior authorization forms; if the prior auth request is submitted electronically, the payer must respond within 24 business hours. Several states prohibit prior auth for “medication-assisted” treatment of opioid dependency.

**“We’re not saying that everyone should go to the newer agents, but if there are medical reasons, there should be an exemptions policy.”**

William C. Reha, MD, MBA

FIGURE / Select state proposals at a glance

<table>
<thead>
<tr>
<th>State</th>
<th>Proposal</th>
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<tbody>
<tr>
<td>NEW JERSEY</td>
<td>Prohibit all payers from requiring pre-approval of any test, procedure, or drug that is covered by the plan</td>
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<tr>
<td>NEW MEXICO</td>
<td>Standardize and streamline the prior authorization process across all health insurers; any prior auth request shall be deemed granted if a final determination is not made within 5 business days</td>
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<tr>
<td>NEW YORK</td>
<td>Shorten the time frame during which an insurer has to determine whether a preauthorization request is medically necessary from 3 business days to 3 days</td>
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<tr>
<td>IOWA</td>
<td>Uniform prior authorization process for all Medicaid managed care plans</td>
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<tr>
<td>ILLINOIS</td>
<td>Uniform prior authorization form for all payers</td>
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<tr>
<td>INDIANA</td>
<td>A health plan that denies prior authorization for a prescription drug must provide a list of acceptable alternatives</td>
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<tr>
<td>KENTUCKY</td>
<td>Insurers must develop processes for electronic prior authorizations</td>
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<tr>
<td>MARYLAND</td>
<td>If a patient who received prior auth for a treatment transitions to a new insurer, the new insurer must likewise authorize the treatment for the entire course of treatment, or 90 days, whichever is less</td>
</tr>
<tr>
<td>WEST VIRGINIA</td>
<td>All payers must develop standardized prior authorization forms; if the prior auth request is submitted electronically, the payer must respond within 24 business hours</td>
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Source: Compiled by Ross E. Weber, American Association of Clinical Urologists
New Products & Services

Male sling redesigned for ease of placement, improved stability

Boston Scientific has launched the AdVanceTM XP Male Sling System, a next-generation, minimally invasive solution for male stress urinary incontinence. The AdVance XP Male Sling System has been redesigned for ease of placement and improved stability and is available in longer sling lengths to accommodate larger patient anatomy. The device leverages the success of the previous AdVance Male Sling System platform, with added benefits including the addition of a chevron anchoring mechanism designed to enhance tissue fixation, changes to the mesh weave intended to provide uniform load displacement, longer sling length to accommodate larger patient anatomy, and helical shaped trocars to better support the male anatomy.

For more information, visit www.bostonscientific.com.

At-home fertility test, sperm storage kit launched

A new at-home fertility test and sperm storage kit, which is FDA-licensed in all 50 states, provides men a low-cost, long-term option for storing young, healthy sperm, according to Dadi, its manufacturer. A patented temperature-controlled at-home fertility test and sperm collection kit each come with a specialized cup, which allows for accuracy and real-time updates throughout the process. To ensure secure end-to-end shipping and delivery, the cup is designed with a unique preservative that protects the customer’s deposit for up to 48 hours and throughout the entire overnight shipping process to Dadi’s cryogenic laboratory. Deposits are then analyzed and cryopreserved in a liquid nitrogen tank at −321°F. Once the process is complete, customers receive a personalized fertility report stating the volume, count, and concentration of the sperm in the deposit. The report also includes a microscopic video of the customer’s actual sperm. Customer information is highly confidential, including the fertility report.

For more information, visit www.dadikit.com.

Novel catheter design has potential to reduce urethral trauma

The FDA has cleared Safe Medical Design, Inc.’s Signal Catheter for commercialization in the United States. Signal Catheter features a novel design and has the potential to reduce urethral trauma as a result of premature balloon inflation during placement, according to the company. Safe Medical Design said it planned to begin distribution as part of its early access program in February 2019.

For more information, visit www.safemedicaldesign.com.

Laboratory licenses urine-based bladder cancer test

Pangea Laboratory recently announced the licensing of a new urine-based laboratory-developed test for bladder cancer detection. Commercialized and sold under the name Bladder CARE, the test is noninvasive, cost-effective, and epigenetic-based, Pangea Laboratory says. Urine samples for the Bladder CARE test can be collected comfortably at home or at the doctor’s office and mailed to Pangea Laboratory for analysis. Pangea Laboratory conducted a pre-clinical collaborative study with Zymo Research, in which 182 urine samples were analyzed using Bladder CARE. The cohort consisted of 97 urine specimens collected from bladder cancer patients and 85 healthy control samples. The study showed that Bladder CARE has 93.8% sensitivity, 85.9% specificity, 88.4% positive predictive value, and 92.4% negative predictive value.

For more information, visit www.pangealab.com.

FDA approves first-in-category assay for Mycoplasma genitalium

The FDA has granted clearance for the Aptima Mycoplasma genitalium assay, an FDA-cleared test to detect this sexually transmitted infection, according to Hologic Inc. The first-in-category assay, cleared through the FDA’s de novo request process, provides laboratories with a highly sensitive and specific molecular diagnostic method to identify infections and enable effective treatment. In published research, Hologic’s ribosomal RNA-based M. genitalium assay displayed greater sensitivity than lab-developed or CE-marked DNA-based tests.

For more information, visit www.hologic.com.

Prostate cancer guide offers information for patients, caregivers

The Prostate Cancer Foundation’s updated 2019 Patient Guide is now available. Compiled with the contributions of leading physicians and researchers in prostate cancer, the guide focuses all of the information available about contemporary prostate cancer research, treatment, and lifestyle factors into a single document. According to the Prostate Cancer Foundation, the guide is for any man who has been newly diagnosed, who is in treatment, or is concerned about a rising PSA. It is also a source of information for loved ones or caregivers, as well as a guide for family members who might want to understand how their shared genes affect their own risk factors.

For more information, visit www.pcf.org.
Are you concerned about dementia as a side effect of ADT?

I’m always concerned about treatment side effects. Androgen suppression, of course, is an essential component of prolonging life for many patients with prostate cancer. But it can certainly impact their quality of life.

There’s mounting evidence that the risk for dementia increases with prolonged use. While impacting only a minority of patients, I think the risk is real. But it’s all about benefits outweighing risks. Knowing how to navigate between quality and duration of life remains one of my biggest challenges. I share that information about any treatment with patients. ADT can prolong life many years; without it men would likely succumb to their disease.

It’s hard to tell if I’m seeing dementia occur in men on ADT because of the patient’s age. Often, patients needing ADT are older, and older patients are at greater risk at baseline for dementia. Now studies are showing that patients on androgen deprivation are at greater risk of developing dementia when they’re older, as well.

So, am I concerned? Yes. Would it be enough for me to stop using it? Usually not.

I do leave the decision to the patient, but as I mentioned, most often the benefit—which is life prolongation—outweighs the risks.

I have a couple of patients who have been on ADT well into their 80s and 90s. When I met them, there was, perhaps, some baseline dementia. ADT might accelerate it, but I can’t tell.”

Matthew McCormack, MD / Reno, NV

I’m not too concerned about it. I think the benefit of androgen deprivation outweighs the risk of side effects. I’ve used androgen deprivation for years and there’s more than one indication for using ADT—one is for metastatic prostate cancer and the other one is adjuvant therapy for either cryosurgery or radiation. For cryosurgery or radiation, the treatment is of very short-term duration. For metastatic prostate cancer, however, you’re talking long-term therapy, and it’s either that or they die from the metastatic disease.

But even with long-term treatment, I haven’t really noticed any dementia developing, to be honest. I’ve read about it, but I have not observed that in my practice.

Patients who need androgen deprivation tend to be older people. Metastatic cancer often occurs in older individuals and older individuals can suffer from dementia.

I have seen other side effects from androgen deprivation—hot flashes, fatigue, and loss of muscle strength—but those aren’t as concerning when you’re considering the longevity ADT can add to the patient’s life, and the use of it definitely prolongs the patient’s life.”

Andrew Wolszczak, MD / Marathon, FL

We are concerned. There is new data coming out demonstrating a potential increase in dementia in men on ADT.

The problem is we don’t have many options in men with advanced prostate cancer. ADT just means depriving the patient of testosterone and has been a main treatment option for years. The old-fashioned method was to do an orchietomy, which was a deforming and permanent procedure. That’s how the whole LHRH-agonist drugs came about. There were alternative treatments like estrogens, but they were associated with heart attack and stroke, so are no longer in use. As we use ADT, we’re having these discussions with patients.

But the increased risk of dementia isn’t restricted to ADT. There’s another class of urologic drugs that’s used very commonly—anticholinergic medications for overactive bladder and urge incontinence. Studies have demonstrated long-term use of anticholinergic medications is associated with an increased risk of cognitive decline and dementia. Most concerning is the fact that some of these effects are not reversible when the medication is stopped. As these medications have been in use for years, they are often generic and inexpensive, and generally covered by health insurance.

Then there’s mirabegron, a beta-3 agonist, which does not seem to be associated with dementia. Unfortunately, as it is newer and more expensive, it can be very difficult to get covered by insurance.

As newer information about potential long-term cognitive side effects is discovered, I try to include this information in my discussion with patients.”

Diane Hartman, MD / Golden, CO

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<table>
<thead>
<tr>
<th>Advertiser Name</th>
<th>Brand/Product</th>
<th>Page #</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accurate Surgical &amp; Scientific Instruments</td>
<td>Microspike</td>
<td>7</td>
<td><a href="http://www.accuratesurgical.com">www.accuratesurgical.com</a></td>
</tr>
<tr>
<td>Astellas</td>
<td>XTANDI</td>
<td>12-16</td>
<td><a href="http://www.xtandihcp.com">www.xtandihcp.com</a></td>
</tr>
<tr>
<td>Boston Scientific</td>
<td>BSC Urology</td>
<td>CV4</td>
<td>bostonscientific.com/beyondstents</td>
</tr>
<tr>
<td>NeoTract</td>
<td>NeoTract/Teleflex</td>
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</tr>
<tr>
<td>Pfizer</td>
<td>Sutent Journal</td>
<td>26-30</td>
<td><a href="http://www.sutenthcp.com">www.sutenthcp.com</a></td>
</tr>
<tr>
<td>Physician Reimbursement Systems</td>
<td>-</td>
<td>19</td>
<td><a href="http://www.prsnetwork.com">www.prsnetwork.com</a></td>
</tr>
<tr>
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<td>Corporate Campaign</td>
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General Urologist Surgeon
Plattsburgh, NY

The Department of Surgery at the University of Vermont College of Medicine is seeking a Clinical Practice Physician in the Division of Urology to join the Champlain Valley Physicians Hospital (CVPH) in Plattsburgh, New York. CVPH is a progressive medical center with nine state-of-the-art OR’s and Ambulatory Surgery Center. This position offers the unique opportunity to work in a community setting while having an active affiliation with Vermont’s only Academic Medical Center; the only ACS verified Level 1 trauma center in the state providing tertiary care to patients from Vermont and Northern NY. Serving the patients from Upstate New York for decades, the local urologic surgery practice recently joined the faculty at the University of Vermont and are now seeking an additional colleague to join the dynamic Urology faculty that span the network hospitals. Specifically, the Division seeks applications from individuals seeking a community Urology practice employment opportunity with a collegial and collaborative setting with University support.

Applicants must be board certified or board eligible and eligible for medical licensure in the state of New York. This is a full-time, 12 month, salaried position.

Plattsburgh is located on the shores of Lake Champlain, near the Adirondack Mountains, Olympic-Lake Placid region, Montreal and Burlington, VT.

The University is especially interested in candidates who can contribute to the diversity and excellence of the academic community through their research, teaching, and/or service. Applicants are requested to include in their cover letter information about how they will further this goal.

The University of Vermont is an Equal Opportunity/Affirmative Action Employer. All qualified applicants will receive consideration for employment without regard to race, color, religion, sex, sexual orientation, gender identity, national origin, disability, protected veteran status, or any other category legally protected by federal or state law. The University encourages applications from all individuals who will contribute to the diversity and excellence of the institution.

Interested individuals should apply online at https://www.uvmjobs.com/postings/31529 (position number 00024781).
Inquiries may be directed to Mark Plante, MD, FRCS(C), FACS, Division Chief, via Kathryn Raymond Kathryn.Raymond@uvmhealth.org.
The Division of Urology at the University of Vermont College of Medicine in alliance with the University of Vermont Medical Center, is seeking a Clinical Practice Physician who is board eligible/board certified Urologist to join the Urology service at our affiliate community medical center, Central Vermont Medical Center (CVMC). This position offers the unique opportunity to work in a community setting while still being involved with an academic center. The successful applicant must have completed an American Board of Urology approved urology residency, be eligible for medical licensure in the State of Vermont and eligible to work in the United States. Duties will include general urologic patient care (adult and minor pediatric) with potential opportunities for the teaching of medical students and urology residents. This is a full-time, 12 month, salaried position with attending staff privileges at Central Vermont Medical Center.

The University is especially interested in candidates who can contribute to the diversity and excellence of the academic community through their research, teaching, and/or service. Applicants are requested to include in their cover letter information about how they will further this goal.

The University of Vermont is an Equal Opportunity/Affirmative Action Employer. All qualified applicants will receive consideration for employment without regard to race, color, religion, sex, sexual orientation, gender identity, national origin, disability, protected veteran status, or any other category legally protected by federal or state law. The University encourages applications from all individuals who will contribute to the diversity and excellence of the institution.

Interested individuals should apply online at http://www.uvmjobs.com/postings/33676 (position number 00023212). Inquiries may be directed to Mark Plante, MD, FRCS(C), FACS, Chief of Urology, Via Kristin Allard Kristin.Allard@uvmhealth.org
The Department of Surgery at the University of Vermont College of Medicine and its affiliated medical centers, the University of Vermont Medical Center and Vermont Children’s Hospital, is seeking a Pediatric Urologic Surgeon. The University of Vermont Medical Center and Vermont Children’s Hospital, along with the university, offers a full spectrum of pediatric medical and surgical specialties. The institution has a Level III NICU, a fully staffed PICU, and serves as the regional adult and pediatric regional trauma center. The Division of Urology holds a long-standing reputation as a premier urologic surgery practice for the surrounding communities’ pediatric and adult patients with urologic care needs and enjoys an excellent relationship with the Department of Pediatrics. With a highly respected residency training program with a robust compliment of dynamic faculty across the network hospitals, the Division seeks applications from individuals seeking an academic career in a collegial and collaborative setting.

Applicants must be BE/BC in Urology and Pediatric Urology, eligible for licensure in the State of Vermont, and eligible to work in the United States. They must have experience in the teaching of medical students and surgical residents, and the clinical and research activities of an academic division of Pediatric Surgery.

This is a full-time, 12-month salaried faculty appointment in the Clinical Scholar Pathway at the rank of Assistant or Associate Professor and carries with it attending staff privileges at University of Vermont Medical Center, a level 1 trauma center that serves as a tertiary care facility serving Vermont and northern New York State. Salary is competitive and commensurate with ability and experience.

Burlington, is located on the eastern shore of Lake Champlain between the Adirondack and Green Mountains, is consistently ranked one of the top places to live and work. Numerous recreational and cultural opportunities across four seasons are available, with Vermont considered to be an outstanding environment to practice medicine.

The University is especially interested in candidates who can contribute to the diversity and excellence of the academic community through their research, teaching, and/or service. Applicants are requested to include in their cover letter information about how they will further this goal.

The University of Vermont is an Equal Opportunity/Affirmative Action Employer. Applications from women, veterans, individuals with disabilities and people from diverse racial, ethnic, and cultural backgrounds are encouraged.

Interested individuals should apply online at https://www.uvmjobs.com/postings/30302 (position number 00024730).

Inquiries may be directed to Mark Plante, MD, FRCS(C), FACS, Division Chief, via Kathryn Raymond Kathryn.Raymond@uvmhealth.org.

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AUA forms PAC to pursue policy goals

PSA access, liability reform, Stark exception top list

With a long list of legislative priorities set for 2019, the AUA has established the AUA Political Action Committee (AUAPAC) to which members can contribute to help advance the association’s advocacy efforts in Washington.

Explaining the purpose of the PAC, AUA President Robert C. Flanigan, MD, said: “AUAPAC helps AUA participate in the political process to advance the specialty of urology and enhance the care of the patients we serve.”

Members’ contributions to AUAPAC will be used to support candidates for the House and Senate, including incumbents, who support the association’s positions and goals with respect to key legislative issues.

Tom Rechtschaffen, MD, chair of the AUA Legislative Affairs Committee, said the new PAC will provide both clinical and academic practice urologists, researchers, allied providers, and others a platform to support candidates and policies impacting urology. A PAC board, comprised of urologists and other leaders with an interest in urology, will guide the nonpartisan AUAPAC, which will follow specific principles and criteria in determining recipients of political contributions.

The AUA previously participated in UROPAC with the American Association of Clinical Urologists (AACU), but pulled out, explained Dr. Rechtschaffen, because of issues involved with two separate organizations involved in its management.

So the AACU took over UROPAC on its own, he said. “But a lot of urologists (who are not AACU members) are excited about legislative affairs and they didn’t really have a place to donate and have their concerns addressed. So, we tried to make sure every urologist is represented. This is why AUAPAC came into existence,” Dr. Rechtschaffen said.

Turnover in legislative priorities

Dr. Rechtschaffen said there has been a “big turnover” in the AUA’s legislative priorities this year, largely because so many previous goals from previous years have been achieved.

Chief among those successes was repeal of the Independent Payment Advisory Board (IPAB), which was included in President Obama’s Affordable Care Act. The plan for IPAB was to make it easier for Congress to control Medicare spending. However, the AUA and the vast majority of organized medicine vehemently opposed IPAB, charging that it would take unilateral action to reduce Medicare reimbursement levels with little recourse for Congress to overturn its actions.

The big chance to finally get rid of IPAB, which never was actually launched, came during consideration of the Bipartisan Budget Act of 2018, which included IPAB repeal language. It was passed by large margins in both the House and Senate and signed into law by President Trump.

Now, the AUA’s priorities include efforts to:

- preserve access to appropriate PSA screening
- reform the U.S. Preventive Services Task Force recommendation process
- promote medical liability reform
- preserve the appropriate use of the in-office ancillary services exception to the Stark Law and work to remove barriers that prevent urologists from participating in value-based payment models
- address work force shortages in all urologic access practice environments, preserve access to appropriate and timely care, expand access to care with innovations including telemedicine, and advocate for increased graduate medical education funding and resources for urology positions
- reduce regulatory burdens (eg, MACRA implementation, prior authorizations, step therapy) and other issues that limit patient access to care, interfere with the physician-patient relationship, or cause physician burnout
- promote urology/cancer research funding
- advocate for the full continuum of care for prostate cancer survivorship
- ensure equitable infertility care for wounded warriors and veterans.

“AUA is still focusing on funding for graduate medical education,” said Dr. Rechtschaffen, who noted that the average age of urologists is the second oldest of any specialty.

“We need to replace those retiring and train more urologists,” he said. “That’s at the top of list. We are also pushing for research funding. The fact is that we cannot find new cures without appropriate funding, and AUAPAC will represent those in research positions who are concerned about this.”

Dr. Rechtschaffen said the AUA also is pushing for fertility benefits for veterans.

“The Veterans Administration has no mechanism to cover fertility treatment, so rectifying this is one of our major initiatives. We are pushing very hard on that.”

Regarding MACRA, he said, “We are all aware that the sustainable growth rate formula was replaced with the MACRA Quality Payment Program, which requires doctors to meet specific criteria for performance and certification for reimbursement. It is a very comprehensive system, and we need to advocate for transparency and simplification of the rules and fairness between specialists and primary care physicians.”

A constantly recurring priority for the AUA is medical liability reform.

“That is always near the top of our member surveys,” Dr. Rechtschaffen said.

These and other issues were included on the agenda of the Annual Urology Advocacy Summit, March 4-6 in Washington.

The conference included speakers ranging from urologists to patients, government employees, and members of Congress. It provided opportunities for participants to meet with lawmakers and their staff and to meet with officials at various federal agencies.

Last year, the summit attracted more than 250 attendees, including physicians and health care professionals from all walks of life.

“The turnout was amazing,” said Dr. Rechtschaffen. “People saw their issues addressed and we got tremendous ratings, especially from the younger physicians who are under the AUA tent, but really don’t know yet what they’ll be doing. Both AACU and LUGPA have helped organize the event and participate in various sessions.

“The fact that all these groups participate make this event special,” he said. “It’s really the whole community, not just the AUA.”
Diagnostic errors still top driver of claims

Changes needed at individual, organizational levels

Diagnostic error continues to be a common and troubling factor in malpractice claims. Consider this case: A 66-year-old female patient with a history of Parkinson’s disease presented to her primary care physician with a complaint of the recent onset of urinary symptoms including frequency and urgency. The primary care physician obtained a urinalysis, which was negative, and referred the patient to a urologist for further follow-up.

The patient presented to the urologist about 5 weeks later, still with the same symptoms. Another urinalysis was done, along with a urine culture, both with a negative result. The urologist attributed the symptoms to the patient’s Parkinson’s disease and continued to see her periodically in follow-up over the next few years.

Over the course of 3 years, the patient’s urinary symptoms continued to deteriorate. She experienced urinary retention proven with bladder ultrasound, and had an episode of hematuria, for which the urologist performed a cystoscopy with no findings. The patient had tried a number of different pharmacologic products over the years for her troubling urinary symptoms. During this 3-year period, the patient’s Parkinson’s disease remained quite stable, though she had reported complaints of fatigue and unintended weight loss.

One summer evening, the patient presented to a local emergency department with a complaint of dysuria and blood in her urine for 3 days. A urinalysis confirmed this and she was discharged home with a prescription for antibiotics and phenazopyridine (Pyridium) for a presumed urinary tract infection with instructions to follow-up with her urologist.

Stage III cancer diagnosed

The patient returned to the urologist within the week and was scheduled for a computed tomography scan in 4 weeks. The CT demonstrated a large (7-cm) right renal mass, which was ultimately diagnosed as Stage III with involvement of the adrenal gland. Despite efforts at surgical and medical management, the patient died less than 2 years later.

A battle of expert witnesses ensued in pre-trial motions for summary judgment. The expert for the defendant urologist affirmed that the urologist did not depart from good and accepted medical practice in failing to order imaging earlier on the patient or further work up the patient for her complaints of fatigue and weight loss, in the setting of both hematuria and Parkinson’s disease.

The expert for the plaintiff affirmed that there was a departure from the standard of care in failing to order a CT scan at the time of hematuria and cystoscopy years earlier, and to continue serial imaging given the facts. In addition, the plaintiff’s expert opined that the defendant urologist was negligent in developing a differential diagnosis that included renal tumor, and for failing to further work up the patient given her contemporaneous symptoms of fatigue and weight loss.

Questions of fact remained at the conclusion of pre-trial motions, both motions were denied, and the case went to trial. The jury found for the plaintiff.

At the heart of this case was the appropriate workup and diagnosis of renal cell carcinoma. When to image, when not to image, what other studies to obtain, and what other disciplines to involve in the setting of a progressive neurologic disease were also argued by both plaintiff and defendant. This is just one of many cases across all disciplines of medicine that question diagnostic error.

~30% of claims involve diagnostic error

According to Coverys, a large medical liability insurer, approximately 30% of all malpractice claims involve diagnostic error (bit.ly/diagnosticaccuracy). Of these, claims involving cancer diagnosis were the most prevalent at 27%. The cited Coverys report identified four key steps of the diagnostic process, all of which were implicated in the aforementioned case: history and physical, lab/diagnostic testing, management of referral, and patient follow-up.

A recent report authored by a group of clinicians, educators, and health policy and communication experts sets forth several suggestions for what the authors call a more “Care-Full” attempt at diagnosis (Ann Intern Med 2018; 169:643-5). While diagnostic error may appear to be linked to a single clinician or perhaps two, there are organizational systems and processes that can aid in preventing similar future occurrences.

Visibility level of a diagnostic error varies depending on the culture of an organization. Those where a diagnostic error is associated with shame or impaired clinical judgment are unlikely to benefit from having robust quality assurance and improvement systems where other clinicians can learn about the root causes of the error. Another recommendation is to implement clinical decision support tools available in electronic medical records and automating second reads for critical diagnostic tests. Yet another suggestion for reduction of error, requiring some introspection, is looking at clinician overconfidence in diagnosis and its contribution to error (Am J Med 2008; 121:S2-23).

Where other indicators of medical malpractice claims have decreased over the years, the prevalence of diagnostic error has not changed, calling for more innovating thinking, introspection, and systematic approaches to prevention and shared learning.
The UroLift System procedure is FDA-cleared for the treatment of symptoms due to urinary outflow obstruction secondary to BPH, including lateral and median lobe hyperplasia, in men 45 years of age or older. Results and patient experience may vary. Most common adverse events reported include hematuria, dysuria, micturition urgency, pelvic pain, and urge incontinence. Most symptoms were mild to moderate in severity and resolved within 2 to 4 weeks after the procedure. Consult the Instructions for Use (IFU) for more information.

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