**UROLOGIST BURNOUT**

**Exhaustion jumps, satisfaction slumps**

Ripple effect includes early retirement, reduced work hours, medical errors

Lisette Hilton | UT CORRESPONDENT

National Report—A new study suggests physician burnout is increasing among doctors in many specialties, and the statistics for urology are troubling. Solutions need to go beyond what individual physicians do for themselves to prevent and address burnout. This is a systemwide issue that needs to be addressed, according to the study’s authors, from Mayo Clinic in Rochester, MN and the American Medical Association.

Researchers published an update (Mayo Clin Proc 2015; 90:1600-13) from a 3-year study looking at burnout and work-life balance among U.S. physicians. The study compares data from 2011 to that collected in 2014. The latest survey is based on 6,880 physician responders; just under 2% were urologists.

While the sample of urologists is relatively small, findings about the specialty are notable, according to Tait Shanafelt, MD, a Mayo Clinic hematologist and the study’s first author.

“At the time of our 2011 study, urologists had a below-average rate of burnout among physician specialty disciplines. Between 2011 and 2014, urologists had one of the largest increases in burnout of all specialties [increasing from 41% to 64%],” Dr. Shanafelt said. “In 2014, urology ranked second highest of 24 specialties evaluated [vs. 15th out of 24 in 2011]. Urologists also had a decline in satisfaction with work-life balance, moving from the 15th most favorable score out of 24 specialties to the 23rd most favorable score.”

Overall, 54.4% of the physicians surveyed had at least one professional burnout symptom, compared to 45.5% in 2011. Satisfaction with work-life balance declined, too, going from 48.5% in 2011 to 40.9% in 2014, according to the study.

More than frustrated

Psychiatrist H. Steven Moffic, MD, said burnout has many definitions, including the simple: “Burnout is emotional exhaustion from undue stress.”

The current study authors describe burnout as a syndrome of emotional exhaustion, loss of meaning in work, feelings of ineffectiveness, and a tendency to view people as objects instead of human beings.

Based on the definition, researchers categorized burnout drivers into five dimensions:

**AMONG UROLOGISTS...**

**Prevalence of burnout is up**

<table>
<thead>
<tr>
<th>Year</th>
<th>Ranking*</th>
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<td>2011</td>
<td>15th</td>
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<td>2014</td>
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*Among 24 specialties surveyed
Source: Adapted from Mayo Clinic Proc 2015; 90: 1600-13

**And satisfaction is down**

Physicians also had a decline in satisfaction with work-life balance, moving from the 15th most favorable score out of 24 specialties to the 23rd most favorable score.

For the full article, please turn to page 11

Renal biopsy may alter management in high-risk patients

The role of biopsy in renal masses is evolving. For large renal masses in particular, new data suggest biopsy may change the management of patients with certain high-risk features, according to E. Jason Abel, MD, assistant professor of urology at the University of Wisconsin School of Medicine and Public Health, Madison. Dr. Abel discusses biopsy’s role in small and large renal masses, associated risks, and when patients can be safely observed.

For large renal masses in particular, new data suggest biopsy may change the management of patients with certain high-risk features, according to E. Jason Abel, MD, assistant professor of urology at the University of Wisconsin School of Medicine and Public Health, Madison. Dr. Abel discusses biopsy’s role in small and large renal masses, associated risks, and when patients can be safely observed.
DOCUMENT Results: Multivariate Analysis of Known Risk Factors and Assay Performance

**ConfirmMDx is the Most Significant Independent Predictor for Prostate Cancer Detection on Repeat Biopsy**

**ConfirmMDx for Prostate Cancer**

An epigenetic assay to help distinguish patients who have a true-negative biopsy from those who may have malignant cancer.

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**ConfirmMDx Clinical Validity & Utility**
- ~90% Negative Predictive Value
- Performance of genes and MSP technology published in 45+ studies and tested on ~5,000 patients
- Test performed on prior negative biopsy tissue

**AN EPIGENETIC ASSAY TO IMPROVE PATIENT STRATIFICATION ON THE DECISION FOR REPEAT BIOPSY**

**THE MOST SIGNIFICANT INDEPENDENT PREDICTOR FOR PROSTATE CANCER DETECTION ON REPEAT BIOPSY**

**Odds**

<table>
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<th>Age (0.0563)</th>
<th>PSA (0.2593)</th>
<th>HGPIN (0.7546)</th>
<th>Atypia (0.0465)</th>
<th>ConfirmMDx (&lt;0.0018)</th>
<th>(p-value)</th>
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<tbody>
<tr>
<td>Odds Ratio</td>
<td>3.00</td>
<td>2.50</td>
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**References:**
P

atent dissatisfaction rates of 10% after inflatable penile prosthesis (IPP) placement may appear low but repres
d a significant concern for men. The past decade has seen

of several hundred IPP cases done in centers of excellence by high-volume implanters who pre-

them to keep its practitioners up to date while helping them practice more efficiently.

These appear to be obvious and unavoidable. It is intriguing that some men may experience

an undaunted downturn in their health or relationship situation, or may have no current sexual partner.

Device-related problems. The pump was singled out as a major focus of patient complaints, perhaps
due to the bulky shoulders of the pump disturbing other sensitive structures within

the scrotum or perhaps due to difficult pumping related to tenderness or a “sticky pump” in which fluid

movement becomes impaired. Fortunately, true mechanical problems are rare.

We believe that pumping difficulties result from prolonged periods of inactivity, likely causing fluid sludging and improper valve movement within the pump. To prevent this, we advise daily or at least regular inflation and deflation of the system. To troubleshoot, we have found that an aggressive “forced deflation” two-handed maneuver almost always readjusts the pump without the need for surgical intervention.

Expectations relating to penile length.

We are aware of several reports of long-term complications related to IPP placement, including:

1. Patient health decline and partner issues. Potential health decline may appear low but represents an important concern for men.
2. IPP dissatisfaction rates of 10% after IPP placement may appear low but represent a significant concern for men.
3. The past decade has seen a proliferation of several IPP cases done in centers of excellence by high-volume implanters who presumably optimized their counseling and surgical processes after continual refinement over many years (see article, page 5). These IPP cases are not the only factor in IPP dissatisfaction, as some cases may be attributed to device-related problems.

Device-related problems include:

1. Pump disturbing other sensitive structures within the scrotum or perhaps due to difficult pumping related to tenderness or a “sticky pump” in which fluid movement becomes impaired. Fortunately, true mechanical problems are rare.
2. We believe that pumping difficulties result from prolonged periods of inactivity, likely causing fluid sludging and improper valve movement within the pump. To prevent this, we advise daily or at least regular inflation and deflation of the system. To troubleshoot, we have found that an aggressive “forced deflation” two-handed maneuver almost always readjusts the pump without the need for surgical intervention.
3. Expectations relating to penile length.

Patient satisfaction: What you can anticipate

IPP satisfaction is a key aspect of patient satisfaction following IPP placement.
**BLOG**

**Why urology residents should care about health policy**

Recent events concerning PSA testing are shaking the ground we walk on and highlight the fact that policy matters to urology residents, says UCLA resident Alan L. Kaplan, MD, in his first *Urology Times* blog. Residents, he says, should be actively thinking about how they can get involved in health policy at the local, state, or national level.

READ DR. KAPLAN’S POST AT: [urologytimes.com/policy-matters](http://urologytimes.com/policy-matters)

**FROM OUR EDITORIAL BOARD**

**All urologists want for 2016 is...**

*Urology Times* recently asked members of our editorial board what they hope to see in the world of urology in 2016. Their wide-ranging answers touched on topics such as PSA-based prostate cancer screening, increased patient access to affordable health insurance, and a stem cell implant for the treatment of stress incontinence. Read their wish list. [urologytimes.com/wish-list](http://urologytimes.com/wish-list)

**BLOG**

**Medicine and the market: The price ain’t right**

Henry Rosevear, MD, recently read what he felt was 2015’s best article on the business of health care. It concludes, not surprisingly, that there’s significant price variation for identical services based on geographical area and that markets dominated by a single hospital system have higher prices. Read why Dr. Rosevear says this article is a must-read. [urologytimes.com/price](http://urologytimes.com/price)

**UT FOLLOWER OF THE MONTH**

**@DrEstradaTapia**

Dr. Estrada Tapia, a urologist in Hermosillo, Sonora, Mexico, is the *Urology Times* Twitter follower of the month! To be featured in this section, engage with us.

Our followers tweet about ICD-10 and more

- **Matt Nielsen** @m_e_nielsen
  - Many tips to [twitterchuck](https://twitter.com/twitterchuck) for joining as co-editor of News&Topics section of *urology* contact us to stir the pot w/op/ed style contrib’s.

- **Matt Cooperberg, MD** @dr_coops
  - Moving and extremely well deserved standing ovation for Paul Schellhammer for sharing his own 25-year experience with prostate cancer #su15

- **Henry Woo** @DrHWoo
  - I remember when medical colleagues rejected using fax for communication. Then it was email & then SMS. Same ones (types) rejecting #SoMe.

- **daviesbj** @daviesbj
  - Searching for a ICD-10 code for dreidel injury

**QUESTION FOR JANUARY**

Do you agree with the AMA’s call to ban DTC drug advertising?

Answer the survey online at [urologytimes.com/DTC-survey](http://urologytimes.com/DTC-survey)

**Urology Times Resource Center**

**METASTATIC CASTRATION-RESISTANT PROSTATE CANCER**

Videos, news, and more to help you manage your patients with advanced disease [http://urologytimes.com/CRPCA](http://urologytimes.com/CRPCA)

**Do you agree with the AMA’s call to ban DTC drug advertising?**

**YES** 70%

**NOT SURE** 15%

**NO** 15%
Sexual Dysfunction | Penile length concerns among reasons for not using device

Survey reveals why patients discontinue IPP use

Wayne Kuznar
UT CORRESPONDENT

Springfield, IL—Ten percent of men with penile implants express dissatisfaction with their implant, and 12% either do not use their implant or use it less often than desired, according to data from a patient registry known as PROPPER (Prospective Registry of Outcomes with Penile Prostheses for Erectile Restoration).

The most common reasons given for not using the implant or using it less than desired are penile length concerns, problems with the pump, a decline in health, and partner issues, said first author Tobias Köhler, MD, MPH, at the 2015 AUA annual meeting in New Orleans.

The vast majority of studies on implant satisfaction “hover around 90%” for satisfaction, said Dr. Köhler, associate professor and residency program director at Southern Illinois University, Springfield. Those data were single series and retrospective in nature.

At the time of Dr. Köhler’s analysis, the PROPPER registry had 958 patients enrolled from 11 sites in the U.S. and Canada. Patients with malleable implants or inflatable prostheses are included. Patients answered questionnaires at baseline and annual follow-up, including questions about satisfaction with their devices. As part of the survey, patients checked boxes that corresponded to their level of satisfaction, but could also write in reasons for their dissatisfaction or non-use of the devices (or use less often than desired). These responses were abstracted into common themes.

At 1 year, 518 patients had completed follow-up. Ten percent expressed dissatisfaction at 1 year, a finding that remains consistent at 2 years, at which time follow-up data were available for 296 patients.

Reasons for lack of use reported
Twelve percent of the patients reported not using their device (11.6% at 1 year and 12.8% at 2 years). The most common reason cited was device dissatisfaction (2.9% at 1 year follow-up and 3.7% at 2 years). Twelve percent also indicated that they used their device but not as often as desired (10.0% at 1 year; 13.9% at 2 years).

Device dissatisfaction was cited by 1.2% at 1 year and 0.3% at 2 years as the reason for less use than desired. A device problem was given as the reason for less use than desired by 0.8% at 1 year and 0% at 2 years. Reasons other than device dissatisfaction, device problem, and partner disinterest were cited by 8.3% at 1 year and 9.8% at 2 years.

Of those that indicated “other” reasons for not using the device, most referred to problems with the device, most often related to the pump, cited by 26% at 1 year and 42% at 2 years; device dissatisfaction most often related to length, cited by 26% at 1 year and 31% at 2 years; health decline, loss of partner, and partner disinterest were cited by 8.3% at 1 year and 9.8% at 2 years.

Other reasons given for less use than desired were similar to “other” reasons for non-use: health decline (43% at 1 year and 67% at 2 years), device dissatisfaction most often related to length (29% at 1 year; 6% at 2 years); device problems, most often related to the pump (17% at 1 year; 3% at 2 years); and partner issues (15% at 1 year; 22% at 2 years).

“On average, most guys in our series had an 18-cm device with 2 cm of rear tip,” Dr. Köhler said. There was no difference in 1-year satisfaction or dissatisfaction rates when comparing devices with least to most rear tip extenders used.

“Attrition bias is most certainly going to be prevalent in perhaps these overly optimistic rates,” he said. “Some of these guys may not have filled out questionnaires because they were unhappy, and thus dropped out of the study. We have to keep that in mind.”

The data can aid in preoperative counseling of implant candidates and provide a realistic expectation to the patient and provider, he said.

The PROPPER Registry is sponsored and funded by American Medical Systems.

InBrief

Dr. Loeb named to Urology Times Editorial Council

Urology Times is pleased to announce the appointment of Stacy Loeb, MD, MSc, to its Editorial Council, representing the areas of men’s health and prostate cancer.

Dr. Loeb is assistant professor of urology and population health at New York University School of Medicine, New York. An international leader in the field of prostate cancer, Dr. Loeb is the author of more than 200 published peer-reviewed articles and eight book chapters.

She hosts the “Men’s Health Show” on Sirius XM 81 satellite radio.

Dr. Loeb received her medical degree from Northwestern Feinberg School of Medicine, Chicago and completed her residency at Johns Hopkins University, Baltimore.
Future of ED treatment may lie in cell-based therapies

May address need for improved treatments for post-RP sexual dysfunction

Louise Gagnon
UT CORRESPONDENT

Ottawa—The future of erectile dysfunction (ED) management following prostate cancer surgery will likely include novel options, among them cell-based therapies, North American experts in the field predict.

“If any cancer surgery, the goal is cancer control and getting the patient back to as normal a life as possible,” said Anthony Bella, MD, in an interview at the 2015 Canadian Urological Association annual meeting in Ottawa.

Phosphodiesterase-type-5 (PDE-5) inhibitors have demonstrated success in treating ED that results after radical prostatectomy (RP), but there remains an unmet need to treat ED in a proportion of patients who are treated surgically for prostate cancer, said Dr. Bella, assistant professor of urology at the University of Ottawa and associate scientist in neuroscience at the Ottawa Health Research Institute in Ottawa.

“[Tissue repair using stem cells] would redefine the paradigm of ED management.”

ANTHONY BELLA, MD

He discussed the topic in an educational forum on controversial issues in men’s health. Other topics included optimal approaches to preserving erectile function after RP and whether testosterone replacement therapy raises cardiovascular disease risk.

“If nerves are fibrosed, the oral agents won’t work,” he said, adding that intracavernosal injection therapy is underutilized in the post-RP setting for men.

Cell-based therapies may address ED that is refractory to PDE-5 inhibitors and may even have better efficacy than PDE-5 inhibitors, he noted.

“Future therapies to prevent ED need to target the downstream effects of nerve injury or compromised blood flow,” Dr. Bella added.

‘Holy grail’: Stem cells that repair smooth muscle

The “holy grail” of tissue repair would be to use stem cells in the body that can help repair smooth muscle, Dr. Bella explained. One of the growth factors that has proven effective in promoting erectile function subsequent to cavernous injury is glial growth factor-2 (GGF2), which was demonstrated in a rat model (J Sex Med 2015; 12:897-905).

“We can do it in such a way that we recruit the cells to come to the area and do what they are designed to do. We know that tissue and cellular repair are facilitated by using your own stem cells,” Dr. Bella said.

It may be GGF2, energy, or a novel molecule that facilitates cellular repair.

“We would redefine the paradigm of ED management,” he said.

Sources of stem cells could be bone marrow or adipose tissue, said Dr. Bella, but he cautioned that the oncogenic potential of any stem cells would have to be heavily considered in any intervention.

“We are very early when it comes to cell-based therapies. The early studies are designed for safety,” Dr. Bella said.

Discussion participant John Mulhall, MD, MSc, said protection of smooth muscle and the endothelium is a key goal of preserving erectile function after RP and put forth that stem cell therapy may permit the reversal of a complication like venous leak.

Animal data point to the value of pre-treatment of the cavernous nerve injury model, noted Dr. Mulhall (J Sex Med, July 24, 2015). Moreover, recently published research highlights that once-daily tadalafil (Cialis) initiated early on after nerve-sparing RP protects penile length and could play a role in the protection of the cavernous injury that occurs subsequent to nerve-sparing RP (Urology 2015; 85:1090-6).

“Daily Cialis [was shown] to prevent smooth muscle degeneration,” said Dr. Mulhall, director of the male sexual and reproductive medicine program at Memorial Sloan Kettering Cancer Center and professor of urology at Weill Cornell Medical Center, New York.

ED management Ideally be striving to get men back to their baseline erectile function prior to RP and not just producing some degree of erectile function, he said. Ultimately, ED management post RP will likely involve multimodal therapy, he added.

Overlap between urologic, CV health

Clinicians should not routinely dissuade patients with prostate cancer from considering testosterone therapy, but there should be a reasonable lag time before initiating testosterone therapy after prostate cancer treatment, with patients with stable PSA values being better candidates for testosterone therapy.

“Many of us believe that testosterone probably has an anti-inflammatory component effect like PDE-5 inhibitors do,” Dr. Brock stated.

Study: TRT, LUTS not linked

A recent literature review found little evidence that testosterone replacement therapy (TRT) causes de novo or worsening lower urinary tract symptoms and changes in prostate volume (Urology Nov. 23, 2015 [Epub ahead of print]).

The authors, who included 35 trials in their review, also found an absence of high-quality evidence supporting guideline recommendations that TRT is “relatively contraindicated in men with severe-range lower urinary tract symptoms.”
Atezolizumab (MPDL3280A): an investigational, engineered anti-PDL1 antibody

CURRENTLY ENROLLING

Clinical trials in various tumor types for atezolizumab (MPDL3280A)*

Trials for atezolizumab (MPDL3280A), an investigational anti-PDL1 antibody, are currently recruiting patients in various tumor types1:

- **Bladder**
  - NCT02589717 (Ph IV)
  - NCT02450331 (Ph III)
  - IMvigor 010
  - NCT02302807 (Ph III)
  - IMvigor 211

- **Breast**
  - NCT02425891 (Ph III)
  - IMpassion 130
  - NCT02605915

- **Colorectal**
  - NCT02291289

- **Hematologic malignancies**
  - NCT02431208
  - NCT02220842
  - NCT02508870

- **Kidney**
  - NCT02420821 (Ph III)
  - IMmotion 151

- **Lung**
  - NCT02486718 (Ph III)
  - NCT02409355 (Ph III)
  - IMpower 111
  - NCT02409342 (Ph III)
  - IMpower 110
  - NCT02367794 (Ph III)
  - IMpower 131
  - NCT02367781 (Ph III)
  - IMpower 130
  - NCT02366143 (Ph III)
  - IMpower 150
  - NCT02013219

- **Melanoma**
  - NCT01656642

- **Solid tumors**
  - NCT02458638
  - NCT02471846
  - NCT02350673
  - NCT02323191
  - NCT02304393
  - NCT01633970
  - NCT02410512
  - NCT02174172
  - NCT01375842

For more information about the atezolizumab (MPDL3280A) clinical trial program

Visit: Find.AntiPDL1trials.com or ClinicalTrials.gov

Call: Genentech Trial Information
Support Line: 1-888-662-6728 (US only)

Email: global.rochegenentechtrials@roche.com

*Product under investigation has not been approved for use outside of the clinical trial setting. This information is presented only for the purpose of providing an overview of the clinical trials and should not be construed as a recommendation for use of any product for unapproved purposes.

1All trials consistent with information on ClinicalTrials.gov as of November 17, 2015.
Number of pre-op prostate biopsies not linked to outcomes

Cheryl Guttman Krader
UT CONTRIBUTING EDITOR

New York—Number of preoperative biopsies does not appear to have any clinically significant effect on self-reported urinary or erectile function outcomes at 1 year after radical prostatectomy (RP), according to the authors of a recent study.

Their study, which was presented at the 2015 AUA annual meeting in New Orleans and published online in BJU International (June 26, 2015), included men who underwent open or minimally invasive RP for prostate cancer at Memorial Sloan Kettering Cancer Center, New York between 2008 and 2011 and who were potent and continent preoperatively. It identified 2,082 patients, of whom 1,668 (80%) had one biopsy prior to RP, 324 (16%) had two biopsies, and 90 (4%) had three or more biopsies.

As assessed by responses to a web-based survey, approximately one-third of 1,249 men with data on erectile function achieved satisfactory recovery at 12 months postoperatively, defined as an International Index of Erectile Function score ≥22. Among the 1,813 men with data on urinary function, about two-thirds achieved satisfactory recovery at both 6 and 12 months, defined as a urinary domain score ≥17.

Multivariable logistic regression analyses found that when compared to men who had a single biopsy, men who had two biopsies or three or more biopsies were equally likely to have satisfactory erectile function at 12 months and satisfactory urinary function at both 6 and 12 months, reported first author Christopher B. Anderson, MD, who conducted the study as a urologic oncology fellow at Memorial Sloan Kettering.

“Men whose prostate cancer progresses while on active surveillance will have undergone multiple prostate biopsies prior to radical prostatectomy. The findings of our study, however, did not confirm our hypothesis that more preoperative biopsies would be associated with worse postoperative urinary and erectile function,” Dr. Anderson said.

“Currently, therefore, we can tell patients we don’t have a reason to be concerned that undergoing follow-up biopsies during active surveillance will affect their functional outcomes if they do require radical prostatectomy,” he added.

Most study patients not on surveillance

However, Dr. Anderson acknowledged the study has limitations.

“Most of the men in our study were not on active surveillance, and only a small number had three or more biopsies,” he said.

“More research is needed to determine if having three or more biopsies will impact functional outcomes, and we plan to look at this question again after we have collected more data.”

Using the available data, a sensitivity analysis was also performed to determine whether the number of biopsies was associated with any change in erectile or urinary domain score when the scores were modeled as continuous variables. Its results showed that men who had two biopsies had significantly lower urinary function scores at 6 and 12 months compared with men who had only a single biopsy prior to RP.

“We suspect, however, that the differences in scores are unlikely to be clinically meaningful,” said Dr. Anderson, who is currently assistant professor of urology at Columbia University Medical Center, New York.

In addition, pre-specified subgroup analyses were performed that excluded high-risk patients (13% of the cohort) and biopsies performed more than 3 years before RP. The results of those analyses were similar to the findings of the primary analysis.

The hypothesis that more preoperative biopsies could have a negative effect on functional outcomes after RP was explored because of the anecdotal observation that surgery could be more difficult in men who had multiple biopsies.

“We postulated that trauma from biopsy could incite an inflammatory reaction and even infection. These events could lead to fibrosis and injury to the periprostatic vasculature and nerves that could make nerve-sparing more difficult,” Dr. Anderson told Urology Times.

The model covariates were age, smoking status, cardiovascular disease, preoperative PSA, clinical tumor stage, and biopsy Gleason sum.

Evaluating web videos found feasible for RARP peer review

Expert, crowdsourced reviewers consistently agree on lower scoring surgeons

Cheryl Guttman Krader
UT CONTRIBUTING EDITOR

Ann Arbor, MI—Evaluation of online videos is a feasible method for peer review of robot-assisted radical prostatectomy (RARP) surgical skills, according to a pilot project undertaken by the Michigan Urological Surgery Improvement Collaborative (MUSIC).

The research, which was presented at the 2015 European Association of Urology annual congress in Madrid, Spain and has been published online in European Urology (January 2016), also found that compared to practicing urologists, layperson reviewers were similar in their identification of lower-performing surgeons.

“This pilot project is the first time that practicing surgeons’ skill in performing robotic surgery has been prospectively peer-reviewed and also the first time that crowdsourced methodology has been used to assess real surgery,” said first author Khurshid R. Ghani, MD, assistant professor of urology at the University of Michigan, Ann Arbor and co-director of MUSIC.

He explained that the overall aim of the project is to improve the technical quality of RARP throughout Michigan.

“Establishing methodology to assess performance is the first step toward that goal. According to our findings, peer review of online videos is a viable approach and there may be a role for crowdsourcing,” Dr. Ghani said.

The idea of using video review germinated from knowledge of work by the Michigan Bariatric Surgery Collaborative that showed
greater technical skill in bariatric surgery, as rated through surgical video review, correlated with better postoperative outcomes (N Engl J Med 2013; 369:1434-42). To help develop the initiative, the MUSIC Coordinating Center turned to James O. Peabody, MD, a robotic prostatectomy pioneer and staff surgeon at Vattikuti Urology Institute, Detroit, to serve as study lead. In addition, they enlisted Thomas S. Lendvay, MD, of the University of Washington, Seattle, who had done work with crowdsourced review.

Exciting potential ramifications
Dr. Peabody told Urology Times that the research has exciting potential ramifications.

“RARP has become the leading surgical treatment for prostate cancer in the United States, and emerging evidence indicates that individual surgeon skill affects important outcomes of potency, continence, and cancer control,” he said.

“Therefore, we believe assessment of surgeons’ technical skill represents a path toward quality improvement, but it is an area that has been understudied.”

The pilot project included RARP case videos voluntarily submitted by 12 surgeons from the MUSIC collaborative. Each video was edited to a running length ≤10 minutes, containing only segments on bladder neck division, nerve sparing, apical dissection, and urethrovesical anastomosis.

The videos were reviewed by 25 surgical experts from MUSIC and crowdsourced reviewers from the Amazon Mechanical Turk platform using the validated Global Evaluation Assessment of Robotic Skills (GEARS) instrument. In addition, unedited portions of the video pertaining to the anastomosis were assessed using the Robotic Anastomosis and Competency Evaluation (RACE). Surgeon identity was unknown to the reviewers.

The crowd completed 2,531 ratings over a period of just 21 hours. The expert reviewers were given a 2-week turnaround time for their ratings on the lower performing surgeons, the crowd assessment might serve as a first-pass mechanism in the evaluation process.

“This initiative is not about picking winners and losers,” Dr. Peabody said. “We want to raise the bar of RARP for everyone. We think that is an exciting possibility, and we are fortunate that urologists in Michigan have been forward thinking and supported this project.”

With the focus being on quality improvement, there is also a plan to implement coaching and improvement strategies for all surgeons. In the pilot, all urologists who submitted a video were given customized feedback reports. A survey of the peer reviewers also showed the process of reviewing their colleagues’ videos was considered educational.

MUSIC is funded by Blue Cross Blue Shield of Michigan and the study authors said they are grateful to the Value Partnership Program for supporting this collaborative UT.

ASSI Marks Vas Cutting Forceps

Taking advantage of proven vascular surgery techniques, the 15º angle of the Marks Vas Cutting Forceps provides larger lumenal area. This allows for easier anastomosis and improves opportunity for patency. Even if inflammation and/or scarring are present at the anastomotic site, the larger area provides greater chances for successful reversals.
Prostate Cancer

Long-term outcomes excellent regardless of technique

Study: High surgeon volume linked to post-RP outcomes

Cheryl Guttman Krader
UT CONTRIBUTING EDITOR

Rochester, MN—Long-term functional outcomes after radical prostatectomy are excellent, regardless of surgical technique, when the procedure is performed by experienced surgeons at a high-volume center, according to a recent study.

The retrospective analysis, which was presented at the 2015 AUA annual meeting in New Orleans and is in press in European Urology Focus, looked at men with clinically localized prostate cancer operated on from 2009 to 2012 at Mayo Clinic in Rochester, MN or Massachusetts General Hospital, Boston. Based on the hypothesis that there is a relationship between surgeon volume and functional outcomes, only men operated on by a high-volume surgeon (≥25 cases annually) were included. The final cohort was comprised of 1,089 men who underwent robot-assisted surgery, 441 men who had an open procedure, and 156 men who had laparoscopic radical prostatectomy.

Analyses of responses on the Expanded Prostate Cancer Index Composite (EPIC) showed there were no statistically significant differences between surgical groups in the proportions of men who reported a moderate/big problem with overall urinary function (5.1% to 6.8%) or overall sexual function (36.1% to 37.5%) or in responses to other EPIC questions relevant to urinary or sexual quality of life. In addition, surgical technique was not associated with overall urinary or sexual bother in either univariable or multivariable logistic regression models adjusting for differences in case mix between surgical groups.

“Recent population-based data suggested alarmingly high rates of urinary incontinence and erectile dysfunction in men who underwent open or robotic radical prostatectomy. We were interested in investigating patient-reported functional outcomes in a contemporary cohort of men operated on by high-volume surgeons,” said first author Boris Gershman, MD, urologic oncology fellow at Mayo Clinic.

Volume more important than technique

“The take-home message from our study is that when it comes to determining functional outcomes after radical prostatectomy, it is more important that the procedure be done by an experienced surgeon at a high-volume center than what technique is used,” added Dr. Gershman, who worked on the study with R. Jeffrey Karnes, MD, and co-authors.

The men who were included ranged in age from 40 to 74 years at the time of surgery (median 62 years) and completed the EPIC survey at a median of 30.5 months after surgery. About one-third of men had a diagnosis of erectile dysfunction preoperatively, and almost 20% were on treatment for erectile dysfunction.

Gleason score at radical prostatectomy was 6 in about 40% of men, 7 in 54%, and 8-10 in 6%. Eighty-three percent of men had T2 disease, and only 2% had positive nodes.

In the multivariable logistic regression analysis, only age at surgery independently predicted overall urinary function. Age at surgery as well as Gleason score at radical prostatectomy, prostate volume, and being on treatment for erectile dysfunction preoperatively were independent predictors of having a moderate or big problem with sexual function after surgery. Men who received treatment for erectile dysfunction preoperatively reported bother with overall sexual function more frequently than men who did not (55% vs. 34%).

Study: mpMRI predicts lymph node involvement

High-risk characteristics include pre-op PSA, seminal vesicle invasion

Cheryl Guttman Krader
UT CONTRIBUTING EDITOR

Bethesda, MD—A combination of findings on preoperative multi-parametric magnetic resonance imaging (mpMRI) showed good accuracy for predicting lymph node involvement on final pathology in men who underwent robot-assisted radical prostatectomy (RARP) for prostate cancer, reported researchers from the National Institutes of Health, Bethesda, MD.

“Preoperative evaluation of lymph node status is an essential component of staging prior to definitive therapy for prostate cancer,” said Steven Abboud, NIH Medical Research Scholar.

“Our study suggests that for men who are part of a fusion biopsy protocol and undergoing mpMRI, the finding of high-risk features on that imaging may help urologists assess the risk of nodal involvement and decide whether or not to perform extended lymph node dissection during radical prostatectomy,” added Abboud, who worked on the study with Peter Pinto, MD, and co-authors. The findings were presented at the 2015 AUA annual meeting in New Orleans.

mpMRI characteristics associated with having positive lymph nodes were investigated in a retrospective study that reviewed clinical information, mpMRI, and surgical pathology reports for 367 patients who underwent RARP with lymph node dissection between 2007 and 2014. Nineteen men (5%) had positive lymph nodes on postoperative surgical pathology.

On univariate analysis, preoperative PSA, higher clinical stage disease, mpMRI suspicion score, total number of prostate lesions seen on mpMRI, presence of extracapsular extension (ECE) on mpMRI, and seminal vesical invasion (SVI) on mpMRI were all significantly associated with lymph node invasion.

Multivariate logistic regression analysis controlling for confounding variables found preoperative PSA, mpMRI suspicion score, presence of ECE on mpMRI, and presence of SVI on mpMRI were significantly associated with cancer-positive lymph nodes. In a receiver operating curve analysis, the combination of the three mpMRI characteristics predicted lymph node involvement on final pathology with an area under the curve of 0.88, which was higher than PSA alone.

“Our experience shows that some men with lymph node involvement on final pathology have microdisease that may be missed on preoperative CT scans and standard pelvic MRI.”

STEVEN ABBOUĐ

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“Our experience shows that some men with lymph node involvement on final pathology have microdisease that may be missed on preoperative CT scans and standard pelvic MRI,” Abboud told Urology Times.

He suggested that it would be interesting to compare the performance of the MRI characteristics for predicting lymph node involvement against currently used nomograms.
The story for ZYTIGA® has significantly evolved.

Presenting...

mCRPC = metastatic castration-resistant prostate cancer; ADT = androgen-deprivation therapy.

INDICATION
ZYTIGA® (abiraterone acetate) in combination with prednisone is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC).

IMPORTANT SAFETY INFORMATION

Contraindications—ZYTIGA® is not indicated for use in women. ZYTIGA® can cause fetal harm (Pregnancy Category X) when administered to a pregnant woman and is contraindicated in women who are or may become pregnant.

Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess—Use with caution in patients with a history of cardiovascular disease or with medical conditions that might be compromised by increases in blood pressure, hypokalemia, or fluid retention. ZYTIGA® may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Safety has not been established in patients with LVEF <50% or New York Heart Association (NYHA) Class III or IV heart failure (in Study 1) or NYHA Class II to IV heart failure (in Study 2) because these patients were excluded from these randomized clinical trials. Control hypertension and correct hypokalemia before and during treatment. Monitor blood pressure, serum potassium, and symptoms of fluid retention at least monthly.

Adrenocortical Insufficiency (AI)—AI was reported in patients receiving ZYTIGA® in combination with prednisone, after an interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of AI if prednisone is stopped or withdrawn, if prednisone dose is reduced, or if the patient experiences unusual stress. Symptoms and signs of AI may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA®. Perform appropriate tests, if indicated, to confirm AI. Increased dosages of corticosteroids may be used before, during, and after stressful situations.

Hepatotoxicity—Monitor liver function and modify, withhold, or discontinue ZYTIGA® dosing as recommended (see Prescribing Information for more information). Measure serum transaminases [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] and bilirubin levels prior to starting treatment with ZYTIGA®, every two weeks for the first three months of treatment, and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the upper limit of normal (ULN) or the bilirubin rises above three times the ULN, interrupt ZYTIGA® treatment and closely monitor liver function.

Please see additional Important Safety Information on the next pages.

Please see brief summary of full Prescribing Information on subsequent pages.
In men with mCRPC who progressed on ADT, consider ZYTIGA® (abiraterone acetate) first.

Final analysis of the pivotal phase 3 trial.*

Every day tells a story.

IMPORTANT SAFETY INFORMATION

Adverse Reactions—The most common adverse reactions (≥10%) are fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion. The most common laboratory abnormalities (>20%) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia.

*Study Design: ZYTIGA®, in combination with prednisone, was evaluated in a phase 3, randomized, double-blind, placebo-controlled, multicenter trial in patients with mCRPC who had not received prior chemotherapy (N=1,088). Patients were using a luteinizing hormone-releasing hormone (LHRH) agonist or were previously treated with orchiectomy. In the ZYTIGA® arm, patients received ZYTIGA® 1,000 mg orally once daily + prednisone 5 mg orally twice daily. In the placebo arm, patients received placebo orally once daily + prednisone 5 mg orally twice daily. In this study, the co-primary efficacy end points were OS and radiographic progression-free survival (rPFS). Select exclusion criteria included AST and/or ALT ≥2.5X ULN, liver metastases, moderate or severe pain, opiate use for cancer pain, and visceral organ metastases.

†At a prespecified final analysis for OS, 65% (354/546) of patients treated with ZYTIGA® + prednisone compared with 71% (387/542) of patients treated with placebo + prednisone had died.

‡Prednisone, as a single agent, is not approved for the treatment of prostate cancer.

§rPFS was assessed with the use of sequential imaging studies and was defined by bone scan identification of 2 or more new bone lesions with confirmation (Prostate Cancer Working Group 2 [PCWG2] criteria) and/or modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria for progression of soft tissue lesions. Analysis of rPFS utilized centrally reviewed radiographic assessment of progression.

*At the prespecified rPFS analysis, 150 (28%) of patients treated with ZYTIGA® + prednisone and 251 (46%) of patients treated with placebo + prednisone had radiographic progression.
In the final analysis...

**ZYTIGA® (abiraterone acetate) + prednisone achieved a median overall survival (OS) of almost 3 years (34.7 months).**

- **4.4 months improvement in median OS—34.7 months** with ZYTIGA® + prednisone vs **30.3 months** with placebo + prednisone (active compound)

**Co-primary end point**—median OS: hazard ratio (HR)=0.81; 95% CI: 0.70, 0.93; \( P=0.0033 \).

**Co-primary end point**—rPFS: median not reached for ZYTIGA® + prednisone vs a median of 8.28 months for placebo + prednisone; HR=0.425; 95% CI: 0.347, 0.522; \( P<0.0001 \).

With a median 49 months of follow-up, there were no notable changes in the safety profile of ZYTIGA® + prednisone since the previously reported interim analyses.

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**Drug Interactions**—Based on *in vitro* data, ZYTIGA® is a substrate of CYP3A4. In a drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. Avoid concomitant strong CYP3A4 inducers during ZYTIGA® treatment. If a strong CYP3A4 inducer must be co-administered, increase the ZYTIGA® dosing frequency only during the co-administration period [see Dosage and Administration (2.3)]. In a dedicated drug interaction trial, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone.

ZYTIGA® is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8. Avoid co-administration with CYP2D6 substrates with a narrow therapeutic index. If alternative treatments cannot be used, exercise caution and consider a dose reduction of the CYP2D6 substrate drug. In a CYP2C8 drug interaction trial in healthy subjects, the AUC of pioglitazone, a CYP2C8 substrate, was increased by 46% when administered with a single dose of ZYTIGA®. Patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with ZYTIGA®.

**Use in Specific Populations**—Do not use ZYTIGA® in patients with baseline severe hepatic impairment (Child-Pugh Class C).


Learn more today at www.zytigahcp.com.

Every day tells a story.
ZYTIGA® (abiraterone acetate) Tablets

INDICATIONS AND USAGE

ZYTIGA is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have shown disease progression on prior androgen deprivation therapy.

CONTRAINDICATIONS

Pregnancy: ZYTIGA can cause fetal harm when administered to a pregnant woman. ZYTIGA is not indicated for use in women. ZYTIGA is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss (see Use in Specific Populations).

WARNINGS AND PRECAUTIONS

Hypertension, Hyponatremia and Fluid Retention Due to Mineralocorticoid Excess

Excess ZYTIGA may cause hypertension, hyponatremia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition (see Clinical Pharmacology (12.1) in full Prescribing Information). In the two randomized clinical trials, grade 3 to 4 hypertension occurred in 2% of patients, grade 3 to 4 hyponatremia in 4% of patients, and grade 3 to 4 edema in 1% of patients treated with ZYTIGA (see Adverse Reactions). Co-administration of a corticosteroid suppresses adrenocorticotrophic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Use caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hyponatremia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia. Use ZYTIGA with caution in patients with a history of cardiovascular disease. The safety of ZYTIGA in patients with left ventricular ejection fraction <50% or New York Heart Association (NYHA) Class III or IV heart failure (in Study 1) or NYHA Class II to IV heart failure (in Study 2) has not been established because these patients were excluded from these randomized clinical trials (see Clinical Studies (14) in full Prescribing Information). Monitor patients for hypertension, hyponatremia, and fluid retention at least once a month. Control hypertension and correct hyponatremia before and during treatment with ZYTIGA.

Adrenocortical Insufficiency: Adrenal insufficiency occurred in the two randomized clinical studies in 0.5% of patients taking ZYTIGA and in 0.2% of patients taking placebo. Adrenocortical insufficiency was reported in patients receiving ZYTIGA in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations (see Warnings and Precautions).

Hepatotoxicity: In the two randomized clinical trials, grade 3 or 4 ALT or AST increases (at least 5X ULN) were reported in 4% of patients who received ZYTIGA, typically during the first 3 months after starting treatment. Patients whose baseline ALT or AST were elevated were more likely to experience liver test elevation than those beginning with normal values. Treatment discontinuation due to liver enzyme increases occurred in 1% of patients taking ZYTIGA. No deaths clearly related to ZYTIGA were reported due to hepatotoxicity events. Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with ZYTIGA, every two weeks for the first three months of treatment and monthly thereafter. In patients with baseline moderate hepatic impairment receiving a reduced ZYTIGA dose of 290 mg, measure ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient’s baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the ULN, or the bilirubin rises above three times the ULN, interrupt ZYTIGA treatment and closely monitor liver function. Re-treatment with ZYTIGA at a reduced dose level may take place only after return of liver function tests to the patient’s baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN (see Dosage and Administration (2.2) in full Prescribing Information).

The safety of ZYTIGA re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

• Hypertension, Hyponatremia, and Fluid Retention due to Mineralocorticoid Excess (see Warnings and Precautions).
• Adrenocortical Insufficiency (see Warnings and Precautions).
• Hepatotoxicity (see Warnings and Precautions).

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

Two randomized placebo-controlled, multicenter clinical trials enrolled patients who had metastatic castration-resistant prostate cancer who were using a gonadotropin-releasing hormone (GnRH) agonist or were previously treated with orchietomy. In both Study 1 and Study 2 ZYTIGA was administered at a dose of 1,000 mg daily in combination with prednisone 5 mg twice daily in the active treatment arms. Placebo plus prednisone 5 mg twice daily was given to control patients.

The most common adverse drug reactions (≥10%) reported in the two randomized clinical trials that occurred more commonly (≥2%) in the abiraterone acetate arm were fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urticaria, tract infection and contusion.

The most common laboratory abnormalities (≥20%) reported in the two randomized clinical trials that occurred more commonly (≥2%) in the abiraterone acetate arm were anemia, elevated alkaline phosphatase, hyperglycemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hyponatremia.

Study 1: Metastatic CRPC Following Chemotherapy: Study 1 enrolled 1195 patients with metastatic CRPC who had received prior docetaxel chemotherapy. Patients were not eligible if AST and/or ALT ≥2.5X ULN in the absence of liver metastases. Patients with liver metastases were excluded if AST and/or ALT >5X ULN.

Table 1 shows adverse reactions on the ZYTIGA arm in Study 1 that occurred with a ≥2% absolute increase in frequency compared to placebo or were events of special interest. The median duration of treatment with ZYTIGA was 8 months.

Table 1: Adverse Reactions due to ZYTIGA in Study 1

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>ZYTIGA with Prednisone (N=791)</th>
<th>Placebo with Prednisone (N=394)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Muscle and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint swelling/discomfort</td>
<td>29.5</td>
<td>4.2</td>
</tr>
<tr>
<td>Muscle discomfort</td>
<td>26.2</td>
<td>3.0</td>
</tr>
<tr>
<td>General disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>26.7</td>
<td>1.9</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot flush</td>
<td>19.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8.5</td>
<td>1.3</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>6.1</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>5.4</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>10.6</td>
<td>0</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>7.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Nocturia</td>
<td>6.2</td>
<td>0</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fractures</td>
<td>5.9</td>
<td>1.4</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arhythmia</td>
<td>7.2</td>
<td>1.1</td>
</tr>
<tr>
<td>Chest pain or chest discomfort</td>
<td>3.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>2.3</td>
<td>1.9</td>
</tr>
</tbody>
</table>

1 Adverse events graded according to CTCAE version 3.0
2 Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness
3 Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Musculoskeletal discomfort and Musculoskeletal stiffness
4 Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema
5 Includes all fractures with the exception of pathological fracture
6 Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradyarrhythmia, Atrioventricular block complete, Conduction disorder, and Bradycardia

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3 Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Musculoskeletal discomfort and Musculoskeletal stiffness
4 Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema
5 Includes all fractures with the exception of pathological fracture
6 Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradyarrhythmia, Atrioventricular block complete, Conduction disorder, and Bradycardia.
Includes terms Angina pectoris, Chest pain, and Angina unstable.
Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, and Ejection fraction decreased

Table 2 shows laboratory abnormalities of interest from Study 1. Grade 3-4 low serum phosphorus (7%) and low potassium (5%) occurred at a greater than or equal to 5% rate in the ZYTIGA arm.

Table 2: Laboratory Abnormalities of Interest from Study 1

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ZYTIGA Arm (N=791)</th>
<th>Placebo Arm (N=394)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>62.5</td>
<td>0.4</td>
</tr>
<tr>
<td>High AST</td>
<td>30.6</td>
<td>2.1</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>28.3</td>
<td>5.3</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>23.8</td>
<td>7.2</td>
</tr>
<tr>
<td>High ALT</td>
<td>11.1</td>
<td>1.4</td>
</tr>
<tr>
<td>High Total Bilirubin</td>
<td>6.6</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Study 2: Metastatic CRPC Prior to Chemotherapy: Study 2 enrolled 1088 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy. Patients were ineligible if AST and/or ALT ≥2.5X ULN and patients were excluded if they had liver metastases.

Table 3 shows adverse reactions on the ZYTIGA arm in Study 2 that occurred with a ≥2% absolute increase in frequency compared to placebo. The median duration of treatment with ZYTIGA was 13.8 months.

Table 3: Adverse Reactions in ≥5% of Patients on the ZYTIGA Arm in Study 2

<table>
<thead>
<tr>
<th>System/organ Class</th>
<th>ZYTIGA with Prednisone (N=542)</th>
<th>Placebo with Prednisone (N=540)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>General disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>39.1</td>
<td>2.2</td>
</tr>
<tr>
<td>Edema</td>
<td>25.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>8.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>30.3</td>
<td>2.0</td>
</tr>
<tr>
<td>Joint swelling/discomfort</td>
<td>6.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>23.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>11.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot flush</td>
<td>22.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21.6</td>
<td>3.9</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>17.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>11.8</td>
<td>2.4</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>13.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>13.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Falls</td>
<td>5.9</td>
<td>0.0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>12.7</td>
<td>0.0</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>10.7</td>
<td>0.0</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td>10.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>8.1</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Cardiovascular Adverse Reactions: In the combined data for studies 1 and 2, cardiac failure occurred more commonly in patients treated with ZYTIGA compared to patients on the placebo arm (2.1% versus 0.7%). Grade 3-4 cardiac failure occurred in 1.6% of patients taking ZYTIGA and led to 5 treatment discontinuations and 2 deaths. Grade 3-4 cardiac failure occurred in 0.2% of patients taking placebo. There were no treatment discontinuations and one death due to cardiac failure in the placebo group.

In Study 1 and 2, the majority of arrhythmias were grade 1 or 2. There was one death associated with arrhythmia and one patient with sudden death in the ZYTIGA arms and 2 deaths in the placebo arms. There were 7 (0.5%) deaths due to cardiorespiratory arrest in the ZYTIGA arms and 3 (0.3%) deaths in the placebo arms. Myocardial ischemia or myocardial infarction led to death in 3 patients in the placebo arms and 2 deaths in the ZYTIGA arms.

Post Marketing Experience

The following additional adverse reactions have been identified during post approval use of ZYTIGA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Respiratory, Thoracic and Mediastinal Disorders: non-infectious pneumonitis. Musculoskeletal and Connective Tissue Disorders: myopathy, including rhabdomyolysis.

DRUG INTERACTIONS

Drugs that Inhibit or Induce CYP3A4 Enzymes: Based on in vitro data, ZYTIGA is a substrate of CYP3A4.

In a dedicated drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. Avoid concomitant strong CYP3A4 inducers during ZYTIGA treatment. If a strong CYP3A4 inducer must be co-administered, increase the ZYTIGA dosing frequency [see Dosage and Administration (2.3) and Clinical Pharmacology (12.3) in full Prescribing Information].

In a dedicated drug interaction trial, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone [see Clinical Pharmacology (12.3) in full Prescribing Information].

Effects of Abiraterone on Drug Metabolizing Enzymes: ZYTIGA is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8. In a CYP2D6 drug-drug interaction trial, the Cmax and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with CYP2D6 substrates [see Clinical Pharmacology (12.3) in full Prescribing Information].

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone (CYP2C8 substrate) was increased by 46% when pioglitazone was given together with a single dose of 1,000 mg abiraterone acetate. Therefore, patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with ZYTIGA [see Clinical Pharmacology (12.3) in full Prescribing Information].

Table 4 shows laboratory abnormalities that occurred in greater than 15% of patients, and more frequently (≥5%) in the ZYTIGA arm compared to placebo in Study 2. Grade 3-4 lymphopenia (9%), hyperglycemia (7%) and high alanine aminotransferase (6%) occurred at a greater than 5% rate in the ZYTIGA arm.

Table 4: Laboratory Abnormalities in ≥15% of Patients in the ZYTIGA Arm of Study 2

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ZYTIGA (N=542)</th>
<th>Placebo (N=540)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-4</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>38.2</td>
<td>8.7</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia¹</td>
<td>56.6</td>
<td>6.5</td>
</tr>
<tr>
<td>High ALT</td>
<td>41.9</td>
<td>6.1</td>
</tr>
<tr>
<td>High AST</td>
<td>37.3</td>
<td>3.1</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>32.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>17.2</td>
<td>2.8</td>
</tr>
</tbody>
</table>

¹Based on non-fasting blood draws
In an embryo-fetal developmental toxicity study in rats, abiraterone acetate caused developmental toxicity when administered at oral doses of 10, 30 or 100 mg/kg/day throughout the period of organogenesis (gestational days 6-17). Findings included embryo-fetal lethality (increased post implantation loss and resorptions and decreased number of live fetuses), fetal developmental delay (skeletal effects) and urogenital effects (bilateral ureter dilation) at doses ≥10 mg/kg/day, decreased fetal anogenital distance at ≥30 mg/kg/day, and decreased fetal body weight at 100 mg/kg/day. Doses ≥10 mg/kg/day caused maternal toxicity. The doses tested in rats resulted in systemic exposures (AUC) approximately 0.03, 0.1 and 0.3 times, respectively, the AUC in patients.

**Pediatric Use:** Safety and effectiveness of ZYTIGA in pediatric patients have not been established.

**Geriatric Use:** Of the total number of patients receiving ZYTIGA in Phase 3 trials, 73% of patients were 65 years and over and 30% were 75 years and over. No overall differences in safety or effectiveness were observed between these elderly patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

**Patients with Hepatic Impairment:** The pharmacokinetics of abiraterone were examined in subjects with baseline mild (N=8) or moderate (N=8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone increased by approximately 1.1-fold and 3.6-fold in subjects with mild and moderate baseline hepatic impairment, respectively compared to subjects with normal hepatic function.

In another trial, the pharmacokinetics of abiraterone were examined in subjects with baseline severe (N=8) hepatic impairment (Child-Pugh Class C) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone increased by approximately 2-fold and 3-fold in subjects with severe baseline hepatic impairment compared to subjects with normal hepatic function.

No dosage adjustment is necessary for patients with baseline mild hepatic impairment. In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of ZYTIGA to 250 mg once daily. Do not use ZYTIGA in patients with baseline severe hepatic impairment (Child-Pugh Class C). If elevations in ALT or AST >5X ULN or total bilirubin >3X ULN occur in patients with baseline moderate hepatic impairment, discontinue ZYTIGA treatment [see Dosage and Administration (2.1) and Clinical Pharmacology (12.3) in full Prescribing Information].

For patients who develop hepatotoxicity during treatment, interruption of treatment and dosage adjustment may be required [see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions, and Clinical Pharmacology (12.3)] in full Prescribing Information.

**Patients with Renal Impairment:** In a dedicated renal impairment trial, the mean PK parameters were comparable between healthy subjects with normal renal function (N=8) and those with end stage renal disease (ESRD) on hemodialysis (N=8) after a single oral 1,000 mg dose of ZYTIGA. No dosage adjustment is necessary for patients with renal impairment [see Dosage and Administration (2.1) and Clinical Pharmacology (12.3) in full Prescribing Information].

**OVERDOSAGE**

Human experience of overdose with ZYTIGA is limited.

There is no specific antidote. In the event of an overdose, stop ZYTIGA, undertake general supportive measures, including monitoring for arrhythmias and cardiac failure and assess liver function.
Renal biopsy may alter management in high-risk patients

Q: Let’s start by discussing the small renal tumor. In the past, conventional wisdom was that a biopsy doesn’t add very much information. If you’ve already decided that a tumor needs treatment based on imaging, then doing a biopsy will only potentially cause a complication or lead to an indeterminate result. In your mind, which patients should be offered percutaneous biopsy for small renal masses today?

A: That’s an excellent question. I do think we should at least discuss renal mass biopsy with the vast majority of patients who have small renal masses. The biopsy informs patients and improves the decision-making process for treatment. Biopsy ultimately provides more information that allows the surgeon to provide better informed consent for treatment.

Given that about 20% of small renal tumors are benign in almost all surgical series, it’s difficult to make the argument that you can decide if a patient needs treatment based on imaging alone. Simply, biopsy allows identification of some patients with benign tumors, who may be spared unnecessary treatment. Biopsy is especially valuable for older patients with comorbidities or for patients who are poor candidates for nephron-sparing techniques.

Finally, serious complications from percutaneous biopsy are rare in experienced centers, especially when compared to the possible complications from treatment.

Q: Doesn’t improved imaging give us a better idea of whether a tumor might be an oncocytooma or angiomylipoma, most of which are not renal cell cancers in the first place? Or do you still think there are places where we might benefit from biopsy for identifying benign versus cancerous masses?

A: Lipid-poor angiomylipomas and oncocyto mas are two tumors that comprise the majority of benign tumors in surgical series. Imaging has certainly improved the detection of lipid-poor angiomylipomas but is not perfect. If we can identify lipid-poor angiomylipomas or oncocyto mas from biopsy, contemporary studies have demonstrated that treatment can usually be avoided for these benign tumors. However, in younger patients with larger tumors, most experts would agree there’s less of a role for biopsy.

Q: Doesn’t improved imaging give us a better idea of whether a tumor might be an oncocytooma or angiomylipoma, most of which are not renal cell cancers in the first place? Or do you still think there are places where we might benefit from biopsy for identifying benign versus cancerous masses?

A: Definitely. At our institution, we have a close relationship with our radiology department and communicate about patients frequently. Improving future patient outcomes is really dependent on cooperation across disciplines. However, it’s important that urologists continue to maintain ownership of these patients because we are trained to understand the tumor biology of kidney cancer and we follow these patients for years to observe the natural history of renal masses. The practice of urologists performing biopsies is encouraging.

Q: Practicing urologists may be concerned about sending a patient to interventional radiology to do the biopsy and have the urologist take care of the complication. There’s also a concern about the radiologist doing cryotherapy or a percutaneous treatment right in the suite. Does this remain in our purview as urologists?

A: For the patient who has a very limited life expectancy and a very small tumor, it’s probably not helpful to identify whether or not a tumor is cancerous since it will not likely affect their life expectancy. In very young patients, biopsy is also probably not as helpful.

But there are a lot of gray areas, since most patients with renal cell cancer are in their 60s or 70s and are healthy but have some comorbidities or borderline renal function. Patients may choose different treatments if they know that they have a benign tumor or a malignancy. If patients understand that they have cancer, some would feel more comfortable consenting to surgery.

Q: I’ve had a few older patients who are not in great shape say that if they have cancer, they need to identify that for their cancer insurance policy; that’s one of the reasons to do a biopsy. Also, I have had many patients in their 70s ask if a mass can be just followed instead of treating it. What do you tell them?

A: The risk is probably dependent on the institutional experience. In our last 700 patients, we’ve had less than 1% incidence of Clavien III complications—those requiring additional treatment. Most complications are related to bleeding and less than 1% of patients will require blood transfusion or angioembolization.

When you’re doing informed consent with patients, what do you tell them about the risks associated with biopsy?

J. BRANTLEY THRASHER, MD

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E. JASON ABEL, MD

Q: If you believe by imaging that you’re looking at a small, percutaneous tumor, how does biopsy help you risk-stratify patients?

A: Biopsy is not appropriate for everyone and the decision should be made for each patient individually. However, I think it’s important to realize that biopsy is one way to avoid the morbidity associated with overtreatment of small renal masses. Overtreatment is associated with a decrease in renal function and increased cost of treatment. The potential risks associated with biopsy are very small, and it does provide more information to help patients make decisions.

Q: How about women in childbearing years? Would you limit biopsy in those cases too?

A: Most complications are related to bleeding. There are probably two reasons to do a biopsy. First, you may not want to overtreat a patient. Second, if a woman is found to have a renal cell cancer, she might want to see a gynecologic oncologist. Biopsy is probably worth doing if a woman has a small renal mass that you are trying to determine whether it is cancerous or not.

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RENAL BIOPSY
continued from page 11

A: The minority of small renal masses will be aggressive tumors. But if you identify an aggressive tumor in an older patient, you may be more likely to treat it. If you identify a grade 4 or sarcomatoid tumor, even when it’s 2 or 3 centimeters, you may offer aggressive treatment to an older comorbid patient.

Q: Patients also tell me they’ve read that aggressive cancer can actually spread cancer along the needle tract. What do you tell them?

A: That is a very rare, almost theoretical risk with modern techniques. We struggle sometimes with explaining rare events because we can’t define the exact risk. We have not seen tumor seeding our institution in the last 20 years, and there have been very limited reports of it. It’s a theoretical concern, but we know that biopsy tract seeding is a rare event for any cancer that involves doing a biopsy, such as prostate cancer.

Q: When you have an upper pole or lower pole tumor that may be extending into a calix or coming from the calix, do you use an endoscopic approach first before placing needles in those tumors?

A: Yes. More central tumors and those we suspect are urothelial cancers are approached ureteroscopically rather than percutaneously.

Q: How do you see percutaneous biopsy fitting into the large heterogeneous class of renal masses?

A: In the management of locally advanced and metastatic renal cell cancer, there is not a lot of data to guide us how to use biopsy. For large, locally advanced but non-metastatic tumors, extended lymph node dissection certainly benefits some patients but may also be associated with increased morbidity.

Several groups have identified poor prognostic factors for patients who harbor lymph node metastases, including advanced clinical stage, high Fuhrman grade, clear cell renal cell cancer, necrosis in the specimen, and sarcomatoid features. If the primary tumor demonstrates these high-risk features from biopsy, the surgeon has that information prior to surgery, and you can discuss more aggressive surgery preoperatively with the patient.

We know these large heterogeneous renal tumors frequently have areas with different tumor grades and rare aggressive pathologic features, such as sarcomatoid de-differentiation. Prior studies of large renal mass using a standard biopsy technique to obtain multiple cores from a single site may be prone to error from sampling. We presented data at the 2015 AUA annual meeting using a novel multiquadrant technique that obtains multiple samples from different sites in large tumors. Using this technique, we demonstrated a higher detection rate of sarcomatoid features, increasing sensitivity from 11% in prior studies to about 85%, and we had no higher rate of complications with this technique.

Q: In patients with advanced disease, the medical oncologists are asking us to debulk the tumor before immunotherapy. In those cases, is there any reason to proceed with a biopsy?

A: Even with newer therapies, there’s certainly a role for cytoreductive nephrectomy in many patients. However, we know from population-based studies that less than half of patients with metastatic disease undergo a cytoreductive nephrectomy; biopsy definitely has a role in identifying metastatic disease in those patients. Subtyping and getting those patients into appropriate treatment is important because some of the treatments work better than others for clear cell carcinoma.

In patients with metastatic disease, renal mass biopsy using a multiquadrant technique demonstrated fewer non-diagnostic biopsies.

In the future, biopsy may be increasingly utilized to identify metastatic renal cell cancer patients who are unlikely to benefit from nephrectomy. For example, metastatic renal cell cancer patients with sarcomatoid de-differentiation in the primary tumor are known to have exceptionally poor survival and may not benefit from cytoreductive surgery.

Q: At our institution, medical oncologists often question whether a patient is a good candidate for cytoreductive nephrectomy simply because their tumor is advancing so quickly. They advise watching it for another 3 to 6 months. Is biopsy helpful in those cases, or are you simply watching the biological growth of such a tumor?

A: In metastatic patients, biopsy establishes a diagnosis for histologic subtype of renal cell cancer. In patients with non-clear cell sub-

How do you see percutaneous biopsy fitting into the large heterogeneous class of renal masses?

J. BRANTLEY THRASHER, MD

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Please see RENAL BIOPSY, page 14
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RENAL BIOPSY

continued from page 12

A: We presented another study at the 2015 AUA annual meeting evaluating patient and tumor characteristics that were predictive of non-diagnostic findings from biopsy. Factors that may increase non-diagnostic rate are: tumor size, radiologic enhancement, the presence of cystic features, and the distance from the tumor to the skin. We reported a non-diagnostic rate of about 15%, which is similar or less than other large series.

The lack of consensus definitions for “non-diagnostic” biopsy is a source of considerable variability in reported biopsy diagnostic rates. It is important to note that the definition of non-diagnostic should also include biopsies that have only normal renal tissue and have likely “missed the target.” These findings should not be interpreted as benign.

In large renal masses with a standard biopsy technique (multiple cores from one site), approximately 10% to 11% of biopsies are non-diagnostic. Using the multi-quadrant technique to sample several sites within large tumors decreased the non-diagnostic rate to 0% in our experience.

Q: You work at a major institution where people are doing this a lot. How is this relevant to the average private practitioner in a community hospital?

A: I think biopsy is relevant to anyone who sees patients with incidental renal masses, although experience is definitely helpful to get the best results. To maintain good quality of care, discussing the approach to renal mass biopsy with your abdominal or interventional radiologist is important. If the urologist is performing a biopsy in the office, I think it’s important to carefully plan the procedure and begin with less anatomically complex lesions. It’s certainly reasonable to expect good results with renal mass biopsy, just as we do with other complex office procedures.

Q: We know that partial nephrectomies for small renal masses are not done very often by private practitioners. They’re simply doing a radical nephrectomy. If you’re going to approach that surgery laparoscopically, would there be a reason to do a biopsy at the time and potentially avoid a nephrectomy?

A: I think we should always use nephron-sparing and minimally invasive approaches when feasible. If a urologist sees a patient with a small central renal tumor and feels that the patient will need a radical nephrectomy for treatment, biopsy can be especially helpful. In most patients with benign masses such as oncocytoma, active surveillance is a better choice compared to radical nephrectomy.

Q: The average urologist might consider doing a biopsy laparoscopically prior to definitive treatment. Would you recommend that approach?

A: We really believe it’s an advantage to have the pathologic diagnosis before the procedure. Unfortunately, frozen pathology is not always reliable and establishing the diagnosis in patients treated with ablation is critical so that we know how to follow patients afterward.

In large renal masses with a standard biopsy technique, approximately 10% to 11% of biopsies are non-diagnostic. Using the multi-quadrant technique to sample several sites within large tumors decreased the non-diagnostic rate to 0% in our experience.

One other argument against biopsying large masses is that, in many cases, it leads to non-diagnostic results. How often does that happen in your series?

J. BRANTLEY THRASHER, MD

FDA approves PD-1 inhibitor for advanced RCC

The FDA has approved nivolumab (Opdivo) injection, for intravenous use, for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.

Nivolumab is a programmed death-1 (PD-1) immune checkpoint inhibitor that works by targeting the immune system through the PD-1 immune checkpoint pathway. It is the first and only PD-1 inhibitor to deliver significant overall survival in patients with advanced RCC who have received prior anti-angiogenic therapy, according to manufacturer Bristol-Myers Squibb.

The approval was based on the CheckMate -025 study of 821 patients with advanced RCC whose disease worsened during or after treatment with an anti-angiogenic agent. Patients were randomized to receive either nivolumab or everolimus (Afinitor), a current standard of care for advanced RCC. Those treated with nivolumab lived an average of 25 months after treatment initiation versus 19.6 months in those treated with everolimus. Additionally, 21.5% of the nivolumab group experienced a complete or partial shrinkage of their tumors, which lasted an average of 23 months versus 3.9% of the everolimus group, lasting an average of 13.7 months.

The most common side effects associated with the use of nivolumab include weakness and lack of energy, cough, nausea, rash, dyspnea, and arthralgia.
ED, diabetes, and CV risk: Update on treatment, risk reduction

Diabetic men with erectile dysfunction often require aggressive ED therapy, should be assessed for CV risk

Charles Walker, MD  ·  Alfredo Suarez-Sarmiento, MD

Erectile dysfunction (ED) is prevalent and more severe in men with diabetes. Compared to other men with ED, diabetics require more aggressive treatment for ED. In this article, we review the etiology and pathophysiology of ED in this challenging patient population and provide an approach to treatment and risk reduction via lifestyle modification and pharmacologic intervention.

Prevalence, etiology of ED in diabetes

Of the commonly recognized causes of erectile dysfunction, diabetes is the second most common behind vascular causes (figure 1). The prevalence of erectile dysfunction in the general population is estimated to be 52% in men between age 40 and 70 years with a staggering 322 million men affected worldwide. According to 2012 U.S. census data, 15.5 million American men have diabetes, 50% of whom have sexual troubles caused by their disease. The prevalence of ED in diabetics is independently associated with duration of diabetes mellitus, occurs 10 to 15 years earlier than in men without diabetes, and is more severe and less responsive to oral treatment than in patients without the disease.

The etiology of ED in diabetics is multifactorial and the determinants of pathogenesis include age, duration of diabetes, degree of glycemic control, presence of microvascular complications, and coexistence of cardiovascular disease. Normal penile erection requires an increase in neurologically mediated cavernosal arterial inflow, cavernosal smooth muscle relaxation, and restriction of venous outflow. Diabetes can cause irreversible damage to vascular endothelium, decreasing blood flow to the penis. Up to 60% to 70% of diabetic men have neuropathy, which impedes neurogenic activation of erections. Cavernosal smooth muscle fibrosis due to chronic inflammation is also common in diabetics and prevents normal smooth muscle relaxation. Inadequate inflow ultimately results in ineffective restriction to outflow.

ED and diabetes: Pathophysiology

Erectile dysfunction in diabetics is mediated by insulin resistance, which leads to endothelial dysfunction and atherosclerosis (figure 2). In epidemiologic studies, worse glycemic control correlates with higher rates of ED, and in animal studies insulin administration relieves diabetes-associated ED and improves surrogates for erectile function (J Urol 2003; 170:291-7). In men without diabetes, the addition of metformin to sildenafil citrate (Viagra) results in improved erectile function, suggesting that insulin regulation is involved in the pathogenesis of vasculogenic ED, even when overt diabetes mellitus is not present (J Androl 2012; 33:608-14).

Diabetes, obesity, and the metabolic syndrome (MetS) are chronic inflammatory states...

Please see ED, DIABETES, page 16

PDE-5 inhibitors remain ‘mainstay’ for ED

continued from page 15

that result in structural damage to the vascular endothelium of the penis and other vascular beds and impaired nitric oxide (NO) release in men with ED. NO causes cavernosal smooth muscle relaxation and inhibits platelet aggregation and adhesion. Reduced bioavailability of NO therefore results in vasoconstriction, platelet adhesion, and smooth muscle cell proliferation, which potentiates the atherosclerotic burden of the penile vasculature, further compromising cavernosal arterial inflow.

Insulin resistance may also cause endothelial dysfunction through an NO-independent pathway mediated by endothelin-1. Insulin stimulates production of endothelin-1, a potent vasoconstrictor, and NO in vascular endothelium. In non-diabetic individuals, the vasodilatory effects of NO predominate; in insulin-resistant states, this does not occur, suggesting that in diabetes there is preservation of endothelin in the face of impaired NO production.

ED, DM, and metabolic syndrome

There is a close link between erectile dysfunction and MetS. MetS is a cluster of conditions that include increased blood pressure, a high blood sugar level, excess body fat around the waist, and abnormal cholesterol levels. These occur together, increasing risk of heart disease, stroke, and diabetes. In the Massachusetts Male Aging Study, ED at baseline predicted subsequent MetS and in a cross-sectional analysis of a cohort of 2,371 men, men over 50 with MetS had a 48% increased risk of severe ED (J Urol 2006; 176:222-6; J Urol 2007; 177: 651–4). Also, prevalence of ED increases as the number of components of MetS increase (Diabetes Care 2005; 28:1201-3).

Testosterone deficiency is independently associated with diabetes and other components of the metabolic syndrome (figure 3). Testosterone deficiency and MetS share multiple comorbidities, including insulin resistance, hyperglycemia, dyslipidemia, and obesity, and both are characterized by common pathophysiologic pathways of inflammation and endothelial dysfunction. What’s unclear is whether low testosterone causes diabetes and components of the MetS, or vice versa. However, the evidence suggests that the relationship is bidirectional. What is clear is that low testosterone should be recognized as an additional independent risk factor for cardiometabolic disease in men with DM and ED.

Treatment of ED in diabetics

The phosphodiesterase type-5 (PDE-5) inhibitors (sildenafil, vardenafil [Levitra], tadalafil [Cialis], avanafil [Stendra]), which work by augmenting nitric oxide, are still the mainstay of treatment for ED. PDE-5 inhibitors require an intact neurologic response and endothelial function, which explains why they are less effective in men with longstanding diabetes. Still, a meta-analysis of 14 randomized controlled trials found a 63% improvement in erectile function in diabetic men taking sildenafil compared to 19% of those taking placebo (Arch Intern Med 2002; 162:1349-60).

Men who have demonstrated suboptimal response to PDE-5 inhibitor therapy should be informed of the benefits and risks of other therapies, including alprostadil intraurethral suppositories (MUSE), vacuum erection devices (VED), intracavernosal drug injection (ICI), and penile prostheses. While response rates to vacuum devices and ICI are good to excellent in diabetic men, compliance rates are poor and dropout rates high. A recent study suggests that diabetic men are more likely to require aggressive therapy for ED, such as insertion of a penile implant (Int J Impot Res 2013; 26:112–5).

Management of CV risk in diabetics with ED

ED is now a well-established precursor of coronary artery disease (CAD) and may predict occult CAD, particularly in men under age 60 years. This is particularly true for men with ED and diabetes, where ED is a strong predictor of silent CAD. A recent study of over 4,500 men with ED found that men with ED and at baseline were more than twice as likely to develop subsequent diabetes than those without ED, suggesting that ED may not only predict CAD but may also predict diabetes in some men (Ann Fam Med 2015; 13:331–5).

Endothelial dysfunction is the link between ED, DM, and CAD; thus the identification and modification of shared risk factors for endothelial function through pharmacologic and/or lifestyle interventions can reduce CV risk while mitigating complications due to diabetes such as ED.

Diabetics, like all men with vasculogenic ED, warrant assessment of cardiovascular risk factors, screening for occult cardiovascular disease, and aggressive modification of atherosclerotic risk factors, especially those with a suboptimal response to PDE-5 inhibition who are likely to be at greatest risk for CAD.

The Yale Cardiovascular and Sexual Health program, a virtual and real-time multidisciplinary collaboration between urology, cardiology, and health psychology, was established to address CV reduction in men with ED, and is comprised largely of men with DM and other
causes of vasculogenic ED. Our approach comprises recommendations originally outlined by the Princeton III Consensus Conference (Mayo Clin Proc 2012; 87:766-8), including: a thorough history emphasizing identification of comorbid conditions, family history, and lifestyle factors; physical examination with attention to waist circumference or BMI, peripheral pulses, and cardiac auscultation; assessment of ED severity and duration; fasting plasma glucose and or hemoglobin A1c; serum creatinine; total testosterone; and plasma lipid levels.

We endorse use of noninvasive risk assessment for all men with (and without) ED and indeterminate or high risk for CVD, which may include one or more of the following at the discretion of our collaborating cardiologist: EKG, cardiac stress test (or in some cases use of emerging biomarkers), and C-reactive protein.

**Lifestyle modification**

Lifestyle modification must be the cornerstone of any effective CV risk-reduction plan in men with ED and diabetes. The benefits of dietary modification in reducing cardiometabolic risk are well established. Numerous studies have demonstrated the association between Mediterranean diet and reduction in overall and cardiovascular mortality. A Mediterranean diet or a diet rich in fruits, nuts, vegetables, and fish and low in red meat has been shown to be associated with lower rates of ED; and conversion to a Mediterranean-style diet improves erectile and endothelial function, and reduces systemic markers of inflammation in men with ED and MetS (Int J Impot Res 2006; 18:405-10).

The benefits of exercise in reducing CV risk and complications of disease among diabetics are well established. Exercise enhances arterial blood flow, which in turn increases endothelial production of NO through shear stress, promotes fat reduction, increases lean muscle mass, reduces insulin resistance, and improves glycemic control and lipid profiles. When combined with dietary or weight loss intervention, moderate physical activity also leads to improvement and preservation of erectile function in diabetics (J Sex Med 2010; 7:156-65).

**Pharmacologic risk reduction**

Data on the dual benefit of pharmacotherapy for CV risk reduction and improvement of ED in men with diabetes, while limited, appear to be promising. In diabetic patients with erectile dysfunction, use of a PDE-5 inhibitor and statin has been shown to decrease the risk of major adverse cardiac events (Int J Androl 2009; 32:587-98). Testosterone replacement therapy (TRT) in hypogonadal diabetic patients may improve cardiometabolic risk and has been shown to decrease CV mortality while improving insulin resistance and central obesity. Reduction in total/LDL cholesterol and triglycerides, improvements in HDL and fasting glucose, and decreased waist circumference have all been observed in men with MetS and DM on TRT. TRT also appears to improve response to PDE-5 inhibitors in diabetic men.

**Summary**

ED is prevalent in men with diabetes and is associated with duration of DM, occurs earlier, and is more severe than in patients without diabetes. ED is an independent risk factor for CAD, and CAD is more severe in diabetics with ED.

Diabetic men are less responsive to oral ED therapies and are likely to require more aggressive therapy for ED. All diabetic men should be assessed for CV risk factors and co-managed with interventions to modify risk and improve erectile function when possible.

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Stressors include drive for relative value units, after-hours call

continued from page 1

excessive workload; inefficiency, encompassing clerical burden; loss of autonomy or control over work; problems with work-life integration; and a loss of meaning in work, according to Dr. Shanafelt.

“Although some dimensions of practice are common to all physicians, others, including hours worked per week, productivity expectations, call schedule, control over work, and other variables can vary by specialty and practice setting,” Dr. Shanafelt said.

“Between 2011 and 2014, urologists had one of the largest increases in burnout of all specialties.”

TAIT SHANAFELT, MD

In general, physicians are prime candidates for burnout. The very traits that led them to pursue medical school might work against them later, according to psychiatrist Merry Noel Miller, MD, author of the book, “Finding Your Emotional Balance: A Guide for Women” (Johns Hopkins University Press).

“Often doctors are competitive and perfectionistic, and they may be very unforgiving with themselves when errors inevitably occur. Their self-doubt can get in the way of developing supportive relationships. The expectations for their time can be limitless, and doctors often adopt attitudes that they must always say yes when asked to do anything. Over time, they can become resentful of this unhealthy lifestyle, and start to acquire an ‘I don’t care’ attitude, instead,” Dr. Miller said.

As for urologists...

It doesn’t surprise Philip M. Hanno, MD, MPH, that urologists are feeling burned out. Dr. Hanno said big stressors include the drive for relative value units (RVUs), resulting in physicians’ being pushed to see significantly more patients in significantly less time.

“And [academic physicians] have less time for doing clinical research, basic research, and the kinds of things that they probably went into academic medicine for,” said Dr. Hanno, professor of urology at the University of Pennsylvania, Philadelphia.

Steven Wahle, MD, a general urologist at the Physicians Clinic of Iowa, a large multispecialty group in Cedar Rapids, said after-hours call is one of the biggest sources of stress among the physicians in his group.

“The after-hours call is very busy. That can really lead to issues with fatigue and lack of sleep. The larger the group, the less the call. But when you’re on call, you’re covering for the whole group, so you have more late-night clinical work,” Dr. Wahle said. “One of the stresses that I hear from all of my partners is that when they are on call, it’s not that the work that is stressful, but the hours are stressful.”

The other big source of stress is the added clerical burden associated with electronic medical records, according to Dr. Wahle.

“It adds about 50 to 90 minutes a day of non-clinical time to finish your clinic notes, and at the hospital we are asked to do more and more clerical tasks,” he said.

“At the hospital, we’re also dealing with increased stressors. Hospital administrators are under the gun right now with reduced reimbursement issues, so they tend to homogenize the OR staff. We’ve lost some of our clinically subspecialized support staff in the OR, so you’re dealing with new people who are unfa-

UT Table

<table>
<thead>
<tr>
<th>Specialty</th>
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<th>2014</th>
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<tbody>
<tr>
<td>Family medicine</td>
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<tr>
<td>General surgery subspecialties</td>
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<td>53%</td>
</tr>
</tbody>
</table>

Source: Adapted from Mayo Clin Proc 2015; 90:1600-13

are on call, it’s not that the work that is stressful, but the hours are stressful.”

STEVEN WAHLE, MD

miliar with the equipment. The ward staff and nurses are becoming younger and younger, with less experience, and they’re less subspecialized in urology, which makes rounding and clinical calls more labor intensive.”

There’s more, he said. Competitive hospital systems are pressuring independent urologists for more and more market share.

“Trying to accommodate referral patterns with the right hospital can be less efficient for our busy schedules, adding to travel time and longer days.” Dr. Wahle said.

Are you burned out?

Doctors who are burning out often begin to lose enthusiasm for work and no longer feel that what they do is meaningful or effective, according to Dr. Shanafelt.

Physicians and others can recognize burnout by the presence of fatigue, cynicism, and a loss of compassion, Dr. Miller pointed out.

Dr. Moffic, who wrote “The Ethical Way: Challenges and Solutions for Managed Behav-

Please see BURNOUT, on page 20
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Ripple effects: Decreased quality of care, increased medical error risk
continued from page 18

The expectations for their time can be limitless, and doctors often adopt attitudes that they must always say yes when asked to do anything.”

MERRY NOEL MILLER, MD

Six tips for preventing burnout

1 Seek balance in life
   “This includes exercise, eating a healthy diet, avoiding excesses [such as alcohol and substance abuse], and especially seeking connection and support from others,” said psychiatrist Merry Noel Miller, MD.
   “It is important for doctors not to isolate themselves, but instead to reach out to others and put a priority on taking care of themselves, as well as their patients.”

2 Become educated about burnout and how to prevent it
   “Preventing it requires working in an environment that does not have too much undue external stress and where one has adequate empowerment to be who one is professionally and personally,” said H. Steven Moffic, MD, a psychiatrist.
   Students might take a course. Some medical schools are teaching future physicians how to prevent burnout in a course called “The Healer’s Art,” created by Rachel Naomi Remen, MD.
   “This course strives to help doctors and students connect to the deep meaning in their work in medicine,” Dr. Miller said.

3 Pay ongoing attention to your well-being
   “Being able to emotionally recoup through adequate time off helps. So does personal meditation, exercise, and ventilation to loved ones, or really any activity that helps one recoup emotionally,” according to Dr. Moffic.

4 Focus on the good
   “Focus on the parts of your day and the parts of medicine that give you satisfaction,” urologist Philip M. Hanno, MD, MPH, said. “I think losing your perspective is one of the biggest issues driving burnout.”

5 Be in the moment
   “I think that being in the moment and not thinking about 100 other things while you’re seeing a patient or while you’re evaluating what you’ve done makes it a much more enjoyable experience,” Dr. Hanno said.

6 Identify stressors and control those you can
   “You’re going to have difficult clinical situations that sometimes have results that you don’t like. That’s part of the business,” said urologist Steven Wahle, MD.
   But physicians can take steps to relieve some of their administrative burdens by delegating this work to staff, hiring more coders, and streamlining electronic medical records software. They can become active on hospital boards and bring to light the issues and need for solutions for their colleagues, according to Dr. Wahle.

“[Academic physicians] have less time for doing clinical research, basic research, and the kinds of things that they probably went into academic medicine for.”

PHILIP M. HANNO, MD, MPH

problematic alcohol use (Arch Surg 2012; 147:168-74), and suicidal ideation (Arch Surg 2011; 146:54-62), according to Dr. Shanafelt.

While burnout is a problem, it isn’t universal. There are many in urology who admit there have been unwanted changes in the profession in recent years, but they don’t feel burned out.

“I think that being in the moment and not thinking about 100 other things while you’re seeing a patient or while you’re evaluating what you’ve done makes it a much more enjoyable experience,” Dr. Hanno said.
Arthur L. Burnett, II, MD, MBA, professor of urology at Johns Hopkins University School of Medicine in Baltimore, said there are more regulations and documentation demands and less freedom to practice now than in the past. But despite these challenges, he doesn’t feel burned out.

“For me, I don’t feel burned out. I feel I’m thriving.”

ARTHUR L. BURNETT, II, MD, MBA

There’s so much variation in what we do every day, from going to the operating room, to seeing patients, to academic pursuits, to clinical research—even if you’re not in academic urology,” Dr. Burnett said. “But there’s no question that we’re under a lot more stress than we were many years ago,” he added.

Solving burnout

The problem is bigger than what individuals can do on their own to prevent and overcome professional burnout, according to Dr. Shanafelt. “Physician burnout is largely a system-based problem and addressing physician burnout is the shared responsibility of physicians and health care organizations,” according to Dr. Shanafelt.

He said health care organizations should focus on improving practice environment efficiency, reducing clerical tasks by transferring them to support staff, and nurturing a practice environment that cultivates flexibility and control.

“Organizational approaches to help physicians optimize meaning in their work and build connections with their colleagues have also been shown to reduce physician burnout in randomized trials,” Dr. Shanafelt said. “In the present study, over 40% of physicians worked more than 60 hours per week as compared to [about] 7% of general U.S. workers.”

Urologists in independent groups and other practice settings need to help identify those colleagues they think might be burning out and reach out, Dr. Wahle said.

“Interactions often are not just a one-on-one relationship with a patient, but also with other people in the hospital, with nurses, or on the floor, or in the office, or in the home. So there is this interconnectedness that is necessary for us to practice, but it also makes us vulnerable in some way. We can be a little burned out from that connection.”

H. STEVEN MOFFIC, MD

“I would say that burnout is the number one problem affecting physicians and medicine today.”

Top challenges facing physicians in 2016

Many of the challenges physicians currently face will continue or even accelerate in 2016. Confusion abounds, driven by uncertainties about issues from shifting payment models to new government mandates to ongoing battles over maintaining certification, according to an article in Medical Economics.

At the same time, the uncertainty and challenges facing health care present opportunities in 2016, the article says. Read on for a glimpse of what lies ahead. For the full article, see bit.ly/2016challenges.

Getting paid what you deserve. Doctors breathed a sigh of relief in April 2015 when Congress and the president came together to pass the Medicare Access and CHIP Reauthorization Act (MACRA), which included a permanent solution for repeated temporary fixes to the Medicare sustainable growth rate methodology.

But that solution came with a price: incentives to move to quality-of-care models for Medicare payments from the old fee-for-service model. Physicians will need to think about adapting to the new models from 2016 through 2019 when implementation of the Merit-Based Incentive Payment System called for in the new law begins.

Affordable Care Act. Republicans in the House of Representatives have tried to repeal the Affordable Care Act (ACA) more than 50 times since the law’s creation, so there’s little doubt the ACA will surface as an election issue in 2016. Republican presidential candidates have called for its repeal while Democratic front-runner Hillary Clinton is proposing tweaks such as a $250 cap on drug costs for patients with chronic or serious illnesses.

But after the country elects a new president next November, it’s doubtful ACA will go away anytime soon, says Chris Sloan, manager at Avalere Health. “Significant aspects [of ACA] have been implemented and interpreted from a regulatory perspective,” Sloan said. Unraveling that, even if a Republican wins the White House, likely will be extremely difficult. Few politicians have the appetite to strip health insurance from the 23 million people who have gained it under the ACA and the expansion of Medicaid it has brought about, he notes.

Payer merger mania. As four of the nation’s biggest health insurers propose merging, the fallout for medical practices and their patients could be tighter controls on practices and higher patient costs.

In a letter to the Justice Department, the American Medical Association opposed the Aetna-Humana and Anthem-Cigna mergers, saying the deals are anti-competitive and will lead to higher consumer costs. Lower reimbursements to physicians by insurance firms as payers consolidate, the organization says, will lead to a competitive and will lead to higher consumer costs. Lower reimbursements to physicians by insurance firms as payers consolidate, the organization says, will lead to higher consumer costs.

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What to include in list of holmium laser codes

Consider whether to list procedures not predominantly performed with laser

Q We are compiling all the CPT codes for capturing usage from hospitals for any time they use a holmium laser. Can you help me with the CPT codes we should be capturing from hospitals? Currently, we have 52214, 52356, 52332, and 52353.

A The holmium is a very versatile laser used to do many procedures in urology, including but not limited to ablation of superficial transitional cell carcinoma, prostate resection, and lithotripsy of urinary calculi.

To our knowledge, the laser is used most commonly in urology for services provided in conjunction with a cystoscope. However, this does not mean that the laser is not used with open procedures, nor does it mean that the laser is not used with other types of services such as laparoscopic services.

The most commonly used codes in which a holmium laser is specifically referenced are:

- **52214**: Cystourethroscopy, with fulguration (including cryosurgery or laser surgery) of trigone, bladder neck, prostatic fossa, urethra, or periurethral glands.
- **52317**: Litholapaxy: crushing or fragmentation of calculus by any means in bladder and removal of fragments; simple or small (less than 2.5 cm)
- **52318**: Litholapaxy: crushing or fragmentation of calculus by any means in bladder and removal of fragments; complex or large (over 2.5 cm)
- **52353**: Cystourethroscopy, with ureteroscopy and/or pyeloscopy; with lithotripsy
- **52356**: Cystourethroscopy, with ureteroscopy and pyeloscopy; with lithotripsy including insertion of indwelling ureteral stent (eg, Gibbons or double-J type)
- **52648**: Laser vaporization of prostate.

You should consider that these codes, while commonly reported when a laser is used, do not require that a holmium laser is used and therefore may include cases without the use of the holmium laser.

Conversely, there are other procedures that can be performed with the laser, such as treatment of strictures at any level in the urinary tract, excision of tumors in the bladder, fulgurations, etc., but are not predominantly performed with a laser.

In the end, if you want to cover all potential procedures, you will need to include a broader list of potential laser codes and then read operative notes to clarify.

Your question included code 52332, which would not require the use of a laser. We are assuming that you are looking at codes that are commonly coded with a laser procedure in your question and would therefore recommend that you leave code 52332 off the search list.

Of course, all medically necessary services that are performed and documented should be coded and charged unless they are bundled by the National Correct Coding Initiative, the payer, or the CPT description.

The provider will need to determine whether other codes describing services provided are bundled, bundled but allowed to be reported with a modifier, or not bundled before reporting all services. Bundled services can be easily checked by entering all codes in the AUA Coding Today bundling matrix. The matrix calculator will explain to you exactly which codes can and cannot be billed. However, it does not sound like you should add code 52332 to your study.

Q What is the difference between CPT codes 74420 and 74450? I have used 74420–26 for retrograde pyelograms for my urologist. Thank you for your help.

A 74420 (Urography, retrograde, with or without KUB) is the correct code to use for the initial reading of an x-ray image in which the urologist injected contrast media into the ureter to visualize the ureters and the kidneys.

You are also correct in using the –26 modifier if the procedure was performed in the hospital or in an ambulatory surgical center, in which the equipment and the technicians belong to and worked for that facility.

74450 (Urethrocystography, retrograde, radiological supervision and interpretation) is the correct code to use for the initial reading of an x-ray image in which the urologist injected contrast media into the lower urinary tract, including the bladder and urethra.

Business of Urology

24 THE BOTTOM LINE

9G to scrutinize eligibility for orders/referrals

26 MONEY MATTERS

The 529 plan: Save for college and reduce taxes

Coding Q&A

Ray Painter, MD, Mark Painter

Urologist Ray Painter, MD, is president of Physician Reimbursement Systems, Inc., in Denver and is also publisher of Urology Coding and Reimbursement Sourcebook. Mark Painter is CEO of PRS Urology SC in Denver.
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 two to four weeks after the procedure.

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The activities of the Office of the Inspector General (OIG) are relevant to the practice of urology, and your ability to mitigate any risk associated with the OIG’s auditing and investigative activities is important. I provided tips for doing so in a series of articles in 2013 and ’14. The OIG recently released its work plan for 2016, and it’s time for an update on what is new, what is not new, and what has been removed in the scope of the office’s intended activities for the coming year and beyond.

As a reminder, OIG is the investigative and enforcement arm of the Department of Health and Human Services (HHS) and its programs, including but not limited to the Centers for Medicare & Medicaid Services and the FDA.

According to its website, the OIG at HHS is the largest inspector general office in the federal government. The primary tools used by the OIG are forced exclusion from HHS programs, civil monetary penalties for violations including kickback and physician self-referral issues, and criminal prosecutions of individuals and businesses for fraud and other egregious acts.

According OIG’s downloadable database as of Dec. 1, 2015, out of a total of 62,678 exclusions, 5,853 physicians and 25 urologists have been excluded from federal programs by the OIG. The top two reasons for exclusions are licensing issues (3,003) and conviction of program-related crimes (1,065).

Each year, the OIG publishes a summary of its activities and a work plan for the coming year. The work plan for fiscal year 2016 includes a number of topics of interest to urologists, which is my focus in this article. For the full report, go to http://bit.ly/OIG2016.

Provider status, imaging
Provider-based status (revised). The OIG continues its focus on “provider-based status,” as hospital-owned physician practices that bill as hospital outpatient departments “can result in higher Medicare payments for services furnished at provider-based facilities and may increase beneficiaries’ coinsurance liabilities.” This area of attention aligns with concerns expressed by the Medicare Payment Advisory Commission and changes to the definition of a hospital-owned practice announced in the recent federal budget. Urology practices that are considering acquisition by a hospital or integrated delivery system should take note.

Medical necessity of high-cost diagnostic radiol-
ory tests (removed) and imaging services payment for practice expenses (retained). In the 2016 work plan, the OIG makes no mention of continuing the focus in previous years on documenting medical necessity for high-cost radiology tests. However, in a related area of the work plan, OIG said it “will review Medicare Part B payments for imaging services to determine whether they reflect the expenses incurred and whether the utilization rates reflect industry practices. For selected imaging services, we will focus on the practice expense components, including the equipment utilization rate.”

Urologists who own diagnostic imaging equipment and render those services to Medicare patients should remain vigilant about documenting the reasons for ordering those tests and review their own utilization rates.

E&M, lab billing, referring/ordering of supplies

Evaluation and management services—inappropriate payments (removed). In its 2015 and 2016 work plans, the OIG omitted the language related to scrutiny of evaluation and management services and possible inappropriate payments. Compliant coding and avoiding fraudulent billing remain important expectations for the urology practice, but the OIG has signaled its investigative and enforcement priorities lie elsewhere.

Laboratory tests—billing characteristics and questionable billing (removed), annual analysis of Medicare clinical laboratory payments (retained), and referring/ordering Medicare services and supplies (new). According to the OIG, “Medicare pays more than other insurers for certain high-volume and high-expenditure laboratory tests.” The OIG has broadened its focus on provider ordering beyond laboratory tests, stating that “CMS requires that physicians and non-physician practitioners who order certain services, supplies and/or DME are required to be Medicare-enrolled physicians or nonphysician practitioners and legally eligible to refer/order services, supplies, and DME. If the referring/ordering physician or non-physician practitioner is not eligible to order or refer, then Medicare claims should not be billed.”

Urology practices should review their policies for delegating and documenting “orders” and “referrals” in the electronic or paper chart to ensure they are compliant with this requirement. Practices that own and operate clinical labs should understand that this is an area of attention for the OIG as well as state and local authorities.

Excessive billing of beneficiaries, prolonged services

Physicians and suppliers—Noncompliance with assignment rules and excessive billing of beneficiaries (removed), place-of-service coding errors (removed), and prolonged services/reasonableness of services (new). The OIG takes the position that “prolonged services”—those requiring time beyond the baseline evaluation and management service—should be rare and unusual. In this new focus area, the OIG announces its intention to examine whether payments for those services are appropriate. Urologists considering the use of these codes should understand the level of scrutiny they may incur and be sure to adequately document the necessity and duration of any prolonged service.

Bottom line: Urologists should be familiar with the areas of focus and scrutiny of oversight agencies like the OIG, analyze the relevance/risk to their own practice, and where appropriate, take steps to mitigate or remediate any potential problems. While it’s uncommon for urologists to be convicted of program-related crimes and/or excluded from participating in federal health programs, it can—and has—happened. 

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Flexible state-sponsored accounts accumulate earnings free of federal income tax

Q As a grandparent, how does funding my grandchildren’s college plan impact my estate?

A Saving for college is one of the most daunting financial tasks a family can face, taking as much commitment and careful planning as arranging your estate. But there’s a powerful tool that lets you both put aside money for family members’ educations and reduce your estate’s exposure to taxes.

The 529 plan, named after the section of the Internal Revenue Code authorizing it, allows you to remove wealth from your estate while you steadily accumulate assets to help educate children, grandchildren, nieces, nephews—and even yourself if you’re planning to go back to college. These accounts are particularly useful for grandparents looking for ways to limit the tax hit on a lifetime of wealth accumulation.

You can set up accounts for several grandchildren and reap the same rewards from each account.

There are big tax advantages to 529 college savings accounts. These state-sponsored accounts are allowed to accumulate earnings free of any federal income tax (usually free of state income tax too). Then, when the account beneficiary reaches college age, tax-free withdrawals can be taken to pay for the beneficiary’s qualified college expenses. While 529 accounts are usually set up for children and grandchildren, no family relationship is required. You can set up an account for any college-bound student you want to help.

Section 529 plans accept large lump-sum contributions (over $200,000 in most cases). Smaller installment pay-ins are also accepted. However, there’s an estate tax advantage to making relatively large lump-sum contributions, as contributions to a 529 account reduce your taxable estate.

While 529 accounts are usually set up for children and grandchildren, no family relationship is required.

For federal gift tax purposes, the contributions are treated as completed gifts eligible for the annual gift tax exclusion of $14,000 in 2016. Even better, you can elect to spread a lump-sum contribution over 5 years and thereby immediately benefit from 5 years worth of annual federal gift tax exclusions. You make the election on the federal gift tax return.

For instance, a single grandparent can make a lump-sum contribution of up to $70,000 in 2016 (same as it was in 2015), which is equal to five times $14,000, to a 529 account set up for a grandchild. A married set of grandparents can jointly contribute up to $140,000 ($70,000 times two). If you have several grandchildren, you do this for as many of them as you wish. Gifts up to these amounts won’t reduce your $5.45 million federal gift tax exemption for 2016 if you elect to take advantage of the 5-year spread privilege (this is up from $5.43 million in 2015).

Your $5.45 million federal estate tax exemption is also untouched. However, if you die during the 5-year spread period, a pro-rata portion of the contribution is added back to your estate for federal estate tax purposes.

When funding an account for a grandchild’s college education, you should always be concerned about what will happen to your money if things don’t turn out as expected. After all, your grandchild could decide to do something other than go to college. If that happens, 529 accounts give you good flexibility.

First, the Internal Revenue Code allows you to change account beneficiaries without any federal tax consequences as long as the new beneficiary is a member of the original beneficiary’s family and in the same generation (or a higher generation). For this purpose, an account beneficiary’s first cousin is considered a same-generation family member. That means a grandparent can move money from an account originally set up for one grandchild into an account set up for any other grandchild with no federal income tax, gift tax, or generation-skipping transfer tax consequences.

Finally, what happens if you simply need to get your money back from the 529 account? The federal tax rules permit that too. You’ll be taxed on any withdrawn earnings and be charged a 10% penalty on any withdrawn earnings.

Q What does the term “passive investing” mean?

A Passive investment management typically refers to the use of index mutual funds within a diversified portfolio. Investors utilize passive management because it provides broad market diversification and low relative internal expense ratios. Passive management focuses on a buy and hold strategy within the portfolio, which results in relatively low trading costs despite the large number of security positions within an index portfolio. Passive investing through an index fund also provides significant diversification benefits since index portfolios hold all the stocks comprising their specific asset class universe.

Financial Tips

- The 529 plan allows you to remove wealth from your estate while you steadily accumulate assets to help educate yourself, children, grandchildren, nieces, and/or nephews.
- 529 plans are allowed to accumulate earnings free of any federal income tax (usually free of state income tax too).
- The Internal Revenue Code allows you to change 529-account beneficiaries without any federal tax consequences as long as the new beneficiary is a member of the original beneficiary’s family and in the same generation (or a higher generation).
- Passive investment management typically refers to the use of index mutual funds within a diversified portfolio, a strategy that provides broad market diversification and low relative internal expense ratios.

Money Matters

Joel M. Blau, CFP, Ronald J. Paprocki, JD, CFP, CHBC

Joel M. Blau, CFP, (top) is president and Ronald J. Paprocki, JD, CFP, CHBC, is chief executive officer of MEDIQUS Asset Advisors, Inc. in Chicago. They can be reached at 800-883-8555 or blau@mediqus.com or paprocki@mediqus.com.

Send us your questions

Send your questions about estate planning, retirement, and investing to Joel M. Blau, CFP, c/o Urology Times, at UT@advantast.com.

Questions of general interest will be chosen for publication. The information in this column is designed to be authoritative. The publisher is not engaged in rendering legal, investment, or tax advice.
First patients treated in phase III study of investigational BPH therapy

Peter Gilling, MD, of Urology Bay of Plenty, Tauranga, New Zealand, has treated the first patients in a global phase III clinical study evaluating the safety and effectiveness of the AquaBeam System as compared to the current standard of care, transurethral resection of the prostate. The AquaBeam System, which is being developed by PROCEPT BioRobotics, combines image guidance and robotics to deliver Aquablation, a waterjet ablation therapy that enables targeted, controlled, and heat-free removal of the tissue for the treatment of lower urinary tract symptoms caused by BPH. The WATER study (Waterjet Ablation Therapy for Endoscopic Resection of prostate tissue) is a prospective randomized U.S. investigational device exemption clinical trial of male patients between the ages of 45 and 80 years who have urinary symptoms due to BPH. The study will enroll over 200 patients in up to 20 global sites, including 12 sites in the United States.

Pivotal phase II results announced for cancer immunotherapy

The investigational cancer immunotherapy atezolizumab shrank tumors (objective response rate) in 27% of people with metastatic urothelial carcinoma whose disease had medium and high levels of PD-L1 expression and worsened after initial treatment, according to results from a pivotal phase II study, IMvigor 210. Ninety-two percent of people who responded to atezolizumab continued to respond when the results were assessed. Median duration of response was not yet reached. Adverse events were consistent with those observed in previous studies. Developer Genentech said these data will be submitted to global health authorities and to the FDA under atezolizumab’s breakthrough therapy designation for the treatment of people whose metastatic bladder cancer expresses PD-L1.

Phase III data: LUTS Tx significantly improves IPSS over 12 months

Sophiris Bio Inc. recently announced final results from its phase III “PLUS-1” study of PRX302 as a treatment for lower urinary tract symptoms of BPH. PRX302 demonstrated a statistically significant improvement in International Prostate Symptom Score total score from baseline over 12 months compared to the vehicle-only control group (7.60 vs. 6.58-point overall improvement; \( p=0.043 \)), the primary endpoint of the study. PRX302 continues to demonstrate a favorable safety profile, with no evidence of any treatment-related sexual or cardiovascular side effects, Sophiris Bio reported.

Company to produce investigational PET prostate cancer biomarker

Siemens’ PETNET Solutions Inc. will formulate the VPA1C molecular biomarker 64Cu TP-3805 exclusively for clinical trials for the biopharmaceutical firm NuView Life Sciences, Inc., of Park City, UT. Targeting the VPA1C receptor over-expressed on the surface of malignant cancer cells, 64Cu TP-3805 is being studied for prostate and breast cancer imaging using positron emission tomography/computed tomography (PET/CT) and PET/magnetic resonance imaging. As a 64Cu-labeled peptide with a longer half-life (12.7 hours), 64Cu TP-3805 is better suited for clinical trial distribution across a large geographical area than other commonly used PET radiopharmaceuticals, Siemens AG said in a press release.

FDA allowance announced for investigational clear cell RCC Tx

X4 Pharmaceuticals has announced FDA allowance of the company’s investigational new drug application for the clinical study of X4P-001, the company’s lead drug candidate, in patients with refractory clear cell renal cell carcinoma. X4P-001 is a CXCR4 inhibitor designed to block non-cancerous immunosuppressive and pro-angiogenic cells from populating the tumor microenvironment, thereby restoring anti-tumor immune function. X4 said the first patient in the phase Ib/IIa study is expected to be dosed in the first quarter of 2016, and the study will take place at multiple cancer centers with leading renal cell carcinoma research located in the United States.

Agreement reached to use bladder cancer assay in clinical study

MDxHealth SA reports that it has entered into an agreement with Erasmus University Medical Center Rotterdam (Erasmus MC) for the inclusion of MDxHealth’s AssureMDx for Bladder Cancer, a urine-based, liquid biopsy test, into a prospective clinical study designed to assess the ability of urine-based molecular tests to stratify patients with nonmuscle-invasive bladder cancer (NMIBC) for recurrence monitoring. A total of 2,000 urine samples from 435 patients will be collected in a multicenter, two-arm, prospective randomized clinical trial financed by ZonMw, the Netherlands Organisation for Health Research and Development and Erasmus MC. The study is designed to assess the test’s ability to safely reduce the number of invasive cystoscopies performed during follow-up of patients with NMIBC with a low/intermediate risk of recurrence or progression. The study will also examine whether the addition of urine tests to follow-up of patients with higher risk of recurrence and progression leads to earlier detection of potentially dangerous recurrent cancers. All urine samples will be tested using the AssureMDx assay.

Phase IIa study of infection agent yields positive topline results

Synthetic Biologics, Inc. recently announced positive topline results from the phase IIa study of SYN-004, the company’s candidate designed to protect the gut microbiome from the unintended effects of certain commonly used intravenous beta-lactam antibiotics for the prevention of Clostridium difficile infection and antibiotic-associated diarrhea. Topline results from the 10 ileostomy participants who completed the phase IIa open-label study demonstrated that SYN-004 successfully degraded residual IV ceftriaxone in the chyme without affecting the intended level of ceftriaxone in the bloodstream, Synthetic Biologics reported.

Metastatic renal cell carcinoma agent found safe, well tolerated

Interim clinical data from an ongoing phase IIa study of its novel anti-cancer drug candidate, Archexin, was presented at the 2015 International Kidney Cancer Symposium in Miami. The ongoing phase IIa clinical study is designed to evaluate the efficacy of Archexin in combination with everolimus (Afinitor) to treat metastatic renal cell carcinoma patients and is being conducted in two stages. The interim results show that at the dose levels tested to date, Archexin appeared to be safe and well tolerated, developer Rexahn Pharmaceuticals reported.

Patient enrollment met for studies of female sexual dysfunction drug

Palatin Technologies, Inc. has achieved its patient enrollment target in its two pivotal phase III clinical studies of bremelanotide for the treatment of female sexual dysfunction. Each North American reconnect study is a multicenter (~80 sites), randomized, placebo-controlled, parallel-group, 8-month trial with an open-label extension phase. The clinical trials are designed to randomize approximately 1,100 women (~550 each trial) to evaluate the efficacy and safety of subcutaneous bremelanotide in premenopausal women with hypoactive sexual desire disorder as an on-demand, as-needed treatment.
I would say I’m seeing a slight decrease in the number of men having the PSA done, especially among older guys—those in their 70s and 80s. But I think men in their 50s and 60s who need to get checked are getting checked. Some of that has to do with primary care physicians and the way they practice. Some are checking PSAs less often. So it’s a little different but not a whole lot.

If I saw a trend where guys in their 50s or 60s were coming in with elevated PSAs and hadn’t been checked for a while, that would start to concern me. I haven’t seen that yet, but it’s still early. I don’t know to what degree, but that certainly may happen.

I look at older men on more of an individualized basis, based on their overall health status. After we discuss things, I let them make their own decision. I’m glad to check it if they want. I think the primary care doctors are checking them less often, so now we’re pretty much just waiting to see what happens."

**Todd Johnson, MD**
Overland Park, KS

"There’s some decrease in screening by primary care physicians, but having said that, I can’t say more of the patients we see with elevated PSAs result in an increase in our positive biopsy rate. I haven’t seen a stage migration yet resulting from the screening delays. We continue to be advocates of screening followed by more nuanced actions based on the PSA.

We may not biopsy a person at the first sign of an elevated PSA. But we certainly recommend that when a PSA is rising too rapidly, or is just too high for their age, patients be biopsied. We’re a pretty localized community in a one-hospital town. In the 30 years we’ve been here, we’ve pretty well educated our primary care physicians and brought them along with the philosophy of PSA screening.

There certainly is a group of primary care physicians that has gotten on the no-screening bandwagon, but that’s not predominating, so I’m not getting a sense that a lot fewer men are being tested.

We’ve always been proactive in getting information out to our patients. We sent an email to our patients that we do believe in screening, and we’ve tightened our indications for biopsy because you can’t ignore a disease that still kills tens of thousands of men a year.

There’s a lot of Gleason 6 PSAs that can be monitored without treatment and people who present with 7s and above who, despite treatment, seem to progress. So where do we really impact the disease? In every other tumor model, there’s a point in time when the tumor was confined to its organ of origin. We’re trying to determine which prostate tumors have the potential to spread and metastasize. We want to identify those cancers that pose a threat early enough, so we can impact survival.

But tell you what: Talk to me in about 3 years. With prostate cancer, that’s the minimum time we’re talking about to determine the effect of our actions."

**William T. Hennessy, MD**
Danbury, CT

"We’re definitely seeing fewer men referred for elevated PSAs. The number of biopsies we’re doing is also down as a result.

Men who do come in are more likely to come in with higher PSAs and we find when we do biopsies, we are more likely to find more advanced prostate cancer as well.

This is definitely concerning. There is a lot of controversy over PSA testing, but to just throw out everything and go back to the pre-PSA era is not the right thing to do. Rather than giving up on it, we have to be smarter about who we’re screening and when we do biopsies. We’ve got extra tools now that make it a little more accurate and help us risk stratify patients better.

For a lot of primary care physicians, it’s a really bewildering issue, and for good reason. Nobody can really give you a straight answer about what we should do and when we should do it.

Because the family practice organization recommended against PSA screening even before the task force came out against it, family practice physicians seem a little more confident in their decision not to do PSA screening, as opposed to other primary care docs who are a bit more confused and want to make sure they are doing the right thing.

I practiced in a smaller community in Maine for 15 years before coming to California. Some primary cares there were responsive; others were incredibly vocal. They would basically imply that I was just case hunting, looking for money. In California, it seems primary care docs are a little more likely to screen."

**Richard Long, MD**
Concord, CA
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AUA lobbies USPSTF on draft research plan

Urology ‘noticeably absent’ from PSA panel, Dr. Wolf says

Washington—The U.S. Preventive Services Task Force (USPSTF), which in 2012 recommended against PSA-based screening for prostate cancer, is developing a new research plan for updating recommendations that urology practices will be expected to follow once it is finalized.

The USPSTF posted information about the project in late October 2015 and invited public comments through Nov. 25, a time frame that coincided with the publication of data in the Journal of Urology (2015; 194:1587-93) and JAMA (2015; 314:2054-61; and 2015; 314:2077-9) pointing to the recommendation’s detrimental effects on diagnosis and treatment. PSA screening has also been in the headlines recently due to a controversial quality measure proposed by the Centers for Medicare & Medicaid Services that would potentially penalize providers for ordering PSA tests. (For more on this measure, see urologytimes.com/PSA-measure.)

AUA, others submit comments

Among comments submitted to USPSTF regarding its new research plan were those from the AUA, which urged close consultation with urology and offered numerous specific recommendations and alterations, and the nonprofit Prostate Cancer International (PCI), which cited “major omissions” in the proposed plan.

“The screening process... might be viewed instead as an algorithm that may include PSA testing, biopsy and appropriate imaging to improve diagnostic accuracy.”

J. STUART WOLF, JR., MD

Dr. Wolf said the AUA and its members “strongly believe that blanket statements regarding PSA testing directed at the entire male population disregard the published benefits associated with such testing in men who may be at higher risk than the average male; as such, we applaud USPSTF in its efforts to incorporate risk stratification into its recommendations regarding PSA testing.”

Some key points offered by the AUA for development of the new policy:

- The AUA supports investigation of using a baseline PSA prior to the potential onset of other conditions that may affect PSA, such as BPH, as a strategy for risk stratification. “Modeling data has shown that such a baseline can be used to guide alternative screening strategies for prostate cancer and lead to reductions in false positive tests and overdiagnosis,” Dr. Wolf wrote.
- The definition of morbidity should be expanded to include the side effects from the use of androgen deprivation therapy.
- Both the positive and negative values of PSA need to be considered in reference to the screening test itself and not just the potential biopsy. “The screening process can be viewed as more than just a PSA,” said Dr. Wolf, “and might be viewed instead as an algorithm that may include PSA testing, biopsy and appropriate imaging to improve diagnostic accuracy.”

In his comments, Dr. Wolf pointed out that the treating physician’s duty is “to present the best available data on the benefits/harms associated with PSA testing, and this can only be presented through appropriate risk stratification. Ultimately, the final decision to undergo PSA testing is left to the patient and his own interpretation of the balance between risks and benefits.”

As such, he encouraged the USPSTF “to pursue additional research into how a patient assesses that risk/benefit trade-off and, ultimately, makes a decision as to whether or not he should be tested.”

PCI lists omissions

Some of the omissions identified by PCI included the following:

- The plan and related research questions fail to discriminate between the benefits and harms associated with drawing blood for PSA testing and the process of making decisions based on PSA test results.
- A “major omission” is the failure to mention the value of digital rectal examinations in association with PSA testing.
- The plan and related research questions fail to address the key issue of the harms and benefits of having a prostate biopsy and “the many things that can be done” to determine whether a biopsy is necessary and ensure that the biopsy’s quality is optimized by the use of MRI scans prior to biopsy.

PCI said it believes USPSTF “is seeking to conduct a serious re-evaluation of the value of screening for prostate cancer based on PSA testing of men who fall into certain appropriate categories.”

Meanwhile, efforts continued on Capitol Hill to enact legislation aimed at reforming the process by which the USPSTF reviews and develops recommendations for clinical preventive services.

The AUA, American Association of Clinical Urologists, and LUGPA are pushing a bill sponsored by Reps. Marsha Blackburn (R-TN) and Bobby Rush (D-IL) that would require that a “balanced representation of primary and specialty care providers” and other key stakeholders in the health care community are involved in the development and review of USPSTF recommendations.

Other changes mandated by the bill would be publishing a draft research plan to guide the systematic evidence review process, considering findings and research by federal agencies and departments, and making the evidence review available for public comment.
 Service of papers indicating you’ve been sued by a patient for medical malpractice is the last thing any provider wants to receive. Aside from invoking stress and anxiety, malpractice suits require time, attention, and preparation, and can remain pending for long periods until full resolution.

In this first installment in a new bimonthly column, I will cover discrete, but important issues that present themselves in medical malpractice suits to best inform the urologic community of their existence and how attorneys may handle them. Knowledge is power. The more you understand about the legal process and workings of a lawsuit, the better equipped you will be to cope with the emotive aspects of a lawsuit, communicate with your attorney, and contribute to your own defense.

This month’s column is the first of two articles focusing on the anatomy of the medical malpractice lawsuit. Part two will address issues related to expert witnesses and the trial itself.

Service of a summons and complaint
A lawsuit alleging medical malpractice will commence with the service of a summons and formal complaint claiming negligence. Receipt of these papers should prompt immediate notice to one’s carrier, providing any documents received (Proc [Bayl Univ Med Cent] 2001; 14:109-12). Complaints in medical malpractice suits commonly allege that a physician failed to conform to applicable standards of care, failed to properly diagnose, failed to properly treat the patient/plaintiff.

There are four components to a negligence claim, each of which the plaintiff must prove (Clin Orthop Relat Res 2009; 467:339-47):

- that the physician owed a duty
- that the physician breached that duty
- the claimed injuries were caused by the breach
- and resulting damages.

It should be noted that the applicable standard of care in a case will depend on the jurisdiction, as states do not have a universal definition of the standard of care (18 American Law Reports 4th 603).

Your attorney will “answer” the complaint. Through the answer, various statements alleged by the plaintiff will be either admitted or denied. In addition, your attorney may assert various affirmative defenses on your behalf. Examples of affirmative defenses may include a violation of the applicable statute of limitations, contributory negligence of the plaintiff, or that the plaintiff failed to mitigate his or her damages. The specific language of affirmative defenses will vary by state.

The discovery phase begins after filing of the lawsuit. During discovery, each party obtains relevant materials, documentation, and records, and these are exchanged between parties. The standard for discovery is broad.

For many physicians, the deposition is the single most memorable encounter with the legal system during the lawsuit.

Generally speaking, information is likely to be discoverable if it is “reasonably calculated to lead to the discovery of admissible evidence.” (73 American Law Reports 2d 12, 15 American Law Reports 3d 1446). Discovery frequently entails the exchange of voluminous documents (often medical records in a medical malpractice action), all of which require careful review by your attorney.

In the case of a plaintiff claiming continuing injuries or damages, the attorney must assure that updated records are received on the plaintiff to evaluate claims of continuing damage. For plaintiffs claiming lost wages, it is crucial to secure employment records and tax returns.

Giving depositions
Once “paper” discovery is complete, it is likely that depositions of the parties will be scheduled. The deposition is a formal proceeding, taken under oath, involving the questioning of a party by an attorney (Clin Orthop Relat Res 2009; 467:339-47). A court reporter will make a record of the entire deposition that will later be used in court, if the case goes to trial. For many physicians, the deposition is the single most memorable encounter with the legal system during the lawsuit (Clin Orthop Relat Res 2009; 467:339-47).

Since the deposition is recorded for use in court at a later date, preparation for a deposition is a critical step in a malpractice case. Take, for example, the following two examples of an answer to the same deposition question:

1. Q. Dr. Perez, does the standard of care require that a urologist prescribe ciprofloxacin for a prostate biopsy?
   A. No.

2. Q. Dr. Perez, does the standard of care require that a urologist prescribe ciprofloxacin for a prostate biopsy?
   A. No, because there is a new Best Practice Policy Statement from the AUA that provides alternative options.

While it may appear that answer two is more appropriate because the urologist is providing information—a defense, really—as to why he or she did not prescribe Cipro for prophylactic treatment, answer one is actually much better. In answer two, the urologist is giving the plaintiff’s attorney more information than what was asked. The plaintiff’s attorney may not know anything about AUA Best Practice Policy Statements, and by answering with superfluous information, you have just tipped off him or her as to where to find additional information that may aid in proving the case.

Don’t help the plaintiff make his or her case. Physicians are educators. Whether you are a urologist in a teaching institution educating medical students and residents or a urologist in private practice educating your patients, leave your educating tendencies at home on the day of your deposition. Answer only what is asked.

Conclusion
Having an understanding of the components of a legal claim and the impact and significance of each phase of the suit should provide urologists with the ability to react appropriately when claims arise and help prevent surprises (Proc [Bayl Univ Med Cent] 2001; 14:109-12).

Knowing what to expect moving forward is comforting, and somewhat analogous to why you never pull a Foley on a Friday.
The most common adverse reactions (≥ 10%) that occurred more commonly (≥ 2% over placebo) in the XTANDI-treated patients from the two randomized clinical trials were asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension, and dizziness/vertigo.

**Study 1: Metastatic Castration-Resistant Prostate Cancer Following Chemotherapy**

Study 1 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 Study 1 that occurred at ≥ 2% in the higher frequency in the XTANDI arm compared to the placebo arm.

**WARNINGS AND PRECAUTIONS**

**Seizure**

In Study 1, which enrolled patients who previously received docetaxel, 7 of 800 (0.9%) patients treated with XTANDI experienced a seizure and no patients treated with placebo experienced a seizure. Seizure occurred from 31 to 603 days after initiation of XTANDI. In Study 2, 1 of 871 (0.1%) chemotherapy-naive patients treated with XTANDI and 1 of 844 (0.1%) patients treated with placebo experienced a seizure. Patients experiencing seizure were permanently discontinued from therapy and all seizure events resolved. There is no clinical trial experience re-administering XTANDI to patients who experienced seizure.

Limited safety data are available in patients with predisposing factors for seizure because these patients were generally excluded from the trials. These exclusion criteria included a history of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within the past 12 months, cerebral vascular accident, brain metastases, and brain arteriovenous malformation. Study 1 excluded the use of concomitant medications that may lower the seizure threshold, whereas Study 2 permitted the use of these medications.

Because of the risk of seizure associated with XTANDI use, patients should be advised of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

**Posterior Reversible Encephalopathy Syndrome (PRES)**

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

**ADVERSE REACTIONS**

**Clinical Trial Experience**

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

Two randomized clinical trials enrolled patients with metastatic prostate cancer that has progressed on androgen deprivation therapy (GnRH therapy or bilateral orchectomy), a disease setting that is also defined as metastatic CRPC. In both studies, patients received XTANDI 160 mg orally once daily in the active treatment arm or placebo in the control arm. All patients continued androgen deprivation therapy. Patients were allowed, but not required, to take glucocorticoids.

The most common adverse reactions (≥ 10%) that occurred more commonly (≥ 2% over placebo) in the XTANDI-treated patients from the two randomized clinical trials were asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension, and dizziness/vertigo.

**Study 1: Metastatic Castration-Resistant Prostate Cancer Following Chemotherapy**

Study 1 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 Study 1 that occurred at ≥ 2% in the higher frequency in the XTANDI arm compared to the placebo arm.

| Table 1. Adverse Reactions in Study 1 (cont.) |
|-----------------|-------------|---------|---------|---------|
| **Respiratory Disorders** | | | | |
| Epistaxis | 3.3 | 0.1 | 1.3 | 0.3 |
| **Gastrointestinal Disorders** | | | | |
| * CTCAE v4 |
| * Includes asthenia and fatigue. |
| * Includes dizziness and vertigo. |
| * Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention. |
| * Includes anosmia, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis. |
| * Includes pneumonia, lower respiratory tract infection, bronchitis, and lung infection. |

**Study 2: Chemotherapy-naive Metastatic Castration-Resistant Prostate Cancer**

Study 2 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 reported in Study 2 that occurred at ≥ 2% in the higher frequency in the XTANDI arm compared to the placebo arm.

| Table 2. Adverse Reactions in Study 2 |
|-----------------|-------------|---------|---------|---------|
| **Respiratory Disorders** | | | | |
| * CTCAE v4 |
| * Includes asthenia and fatigue. |
| * Includes dizziness and vertigo. |
| * Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention. |
| * Includes anosmia, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis. |
| * Includes pneumonia, lower respiratory tract infection, bronchitis, and lung infection. |
**Table 2. Adverse Reactions in Study 2 (cont.)**

1. C/Rx: 
   - Includes asthenia and fatigue. 
   - Includes dizziness and vertigo. 
   - Includes arthralgia, memory impairment, cognitive disorder, and disturbance in attention. 
   - Includes dizziness, arrhythmia, and dyspnea. 
   - Includes nausea, vomiting, and constipation. 
   - Includes rash, diarrhea, and anorexia. 

2. Laboratory Abnormalities: 
   - Metabolism by CYP3A4 (e.g., alfentanil, cyclosporine, and CYP2C9 and CYP2C19 inducer in humans. At steady-state, Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C8 inducer with XTANDI cannot be avoided, as enzalutamide may decrease their activity. If co-administration with warfarin cannot be avoided, conduct additional INR monitoring.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**—Pregnancy Category X. 

**Risk Summary**

XTANDI can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. While there are no human data on the use of XTANDI in pregnancy and XTANDI is not indicated for use in women, it is important to know that maternal use of a drug or anandrogen receptor inhibitor could affect development of the fetus. Enzalutamide caused embryo-fetal toxicity in mice at exposures that were lower than in patients receiving the recommended dose. XTANDI is contraindicated in women who are or may become pregnant while taking the drug. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss. Advise females of reproductive potential to avoid becoming pregnant during treatment with XTANDI.

**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 patelnae at 30 mg/kg/day. Doses of 30 mg/kg/day caused maternal toxicity. The doses tested in mice (1, 10 and 30 mg/kg/day) resulted in systemic exposures (AUC) approximately 0.04, 0.4, and 1.1 times, respectively, the exposures in patients. Enzalutamide did not cause developmental toxicity in rabbits when administered throughout the period of organogenesis (gestational days 6-18) at dose levels up to 10 mg/kg/day (approximately 0.4 times the exposures in patients based on AUC).

**Nursing Mothers**

XTANDI is not indicated for use in women. It is not known if enzalutamide is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from XTANDI, a decision should be made to either discontinue nursing, or discontinue the drug taking into account the importance of the drug to the mother.

**Pediatric Use**

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

**Geriatric Use**

Of 1671 patients who received XTANDI in the two randomized clinical trials, 75% were 65 and over, while 31% were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

**Patients with Renal Impairment**

A dedicated renal impairment trial for XTANDI has not been conducted. Based on the population pharmacokinetic analysis using data from 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] < 80 mL/min) compared to patients 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 institute 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, 480 mg, and 600 mg daily. Patients may be at increased risk of seizure following an overdose.

**NONCLINICAL TOXICOLOGY**

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of enzalutamide. 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, hypoperoxidaseogenesis 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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076-1200-PM

**Drugs that Induce CYP3A4**

Co-administration of a strong CYP3A4 inducer (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, and nifedipine) increased the composite area under the plasma concentration-time curve (AUC) of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold. Co-administration of XTANDI with a strong CYP2C8 inhibitor cannot be avoided, as enzalutamide may decrease their activity. If co-administration with warfarin cannot be avoided, conduct additional INR monitoring.

**Drugs that Induce CYP2C8**

Co-administration of rifampin (strong CYP3A4 inducer and moderate CYP2C9 inducer) decreased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 32%. Co-administration of strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, and rifampin) with XTANDI should be avoided if possible. If co-administration of XTANDI with a strong CYP2C9 inhibitor cannot be avoided, reduce the dose of XTANDI.

**Drugs that Inhibit CYP2C8**

Co-administration of a strong CYP2C8 inhibitor (gemfibrozil) increased the composite area under the plasma concentration-time curve (AUC) of enzalutamide plus N-desmethyl enzalutamide (approximately 0.4 times the exposures in patients based on AUC).

**Pediatric Use**

While taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss. Advise females of reproductive potential to avoid becoming pregnant during treatment with XTANDI.

**Animal Data**

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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.
Indication

XTANDI (enzalutamide) capsules is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC).

Important Safety Information

Contraindications

XTANDI is not indicated for women and is contraindicated in women who are or may become pregnant. XTANDI can cause fetal harm when administered to a pregnant woman.

Warnings and Precautions

Seizure

In Study 1, conducted in patients with metastatic castration-resistant prostate cancer (CRPC) who previously received docetaxel, seizure occurred in 0.9% of XTANDI patients and 0% of placebo patients. In Study 2, conducted in patients with chemotherapy-naive metastatic CRPC, seizure occurred in 0.1% of XTANDI patients and 0.1% of placebo patients. There is no clinical trial experience re-administering XTANDI to patients who experienced a seizure, and limited safety data are available in patients with predisposing factors for seizure. Study 1 excluded the use of concomitant medications that may lower threshold; Study 2 permitted the use of these medications. Because of the risk of seizure associated with XTANDI use, patients should be advised of the risk of engaging in any activity during which 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)

In post approval use, there have been reports of PRES in patients receiving XTANDI. PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. Discontinue XTANDI in patients who develop PRES.

Adverse Reactions

The most common adverse reactions (≥ 10%) reported from two combined clinical studies that occurred more commonly (≥ 2% over placebo) in XTANDI patients were asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension, and dizziness/vertigo.

In Study 1, Grade 3 and higher adverse reactions were reported among 47% of XTANDI patients and 53% of placebo patients. Discontinuations due to adverse events were reported for 16% of XTANDI patients and 18% of placebo patients. In Study 2, Grade 3-4 adverse reactions were reported in 44% of XTANDI patients and 37% of placebo patients. Discontinuations due to adverse events were reported for 6% of both study groups.

- Lab Abnormalities: Grade 1-4 neutropenia occurred in 15% of XTANDI patients (1% Grade 3-4) and 6% of placebo patients (0.5% Grade 3-4). Grade 1-4 thrombocytopenia occurred in 6% of XTANDI patients (0.3% Grade 3-4) and 5% of placebo patients (0.5% Grade 3-4). Grade 1-4 elevations in ALT occurred in 10% of XTANDI patients (0.2% Grade 3-4) and 16% of placebo patients (0.2% Grade 3-4). Grade 1-4 elevations in bilirubin occurred in 3% of XTANDI patients (0.1% Grade 3-4) and 2% of placebo patients (no Grade 3-4).

- Infections: In Study 1, 1% of XTANDI patients compared to 0.3% of placebo patients died from infections or sepsis. In Study 2, 1 patient in each treatment group (0.1%) had an infection resulting in death.

- Falls (including fall-related injuries), occurred in 9% of XTANDI patients and 4% of placebo patients. Falls were not associated with loss of consciousness or seizure. Fall-related injuries were more severe in XTANDI patients, and included non-pathologic fractures, joint injuries, and hematomas.

- Hypertension occurred in 11% of XTANDI patients and 4% of placebo patients. No patients experienced hypertensive crisis. Medical history of hypertension was balanced between arms. Hypertension led to study discontinuation in < 1% of all patients.

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.
1450 urologists nationwide have already prescribed XTANDI*1

Learn what XTANDI can offer you and your patients at XtabdiHCP.com.

*This is the number of urologists who have prescribed XTANDI since FDA approval (August 31, 2012).

**Indication:** XTANDI (enzalutamide) capsules is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC).

**Select Safety Information:** XTANDI is not indicated for use in women. XTANDI is contraindicated in women who are or may become pregnant.

**Reference:** 1. Data on file as of September 2015, Astellas Pharma US, Inc.

Please see inside page for additional Important Safety Information. Please see adjacent pages for Brief Summary of Full Prescribing Information.