SHOCK WAVE LITHOTRIPSY
Down, but not out
Noninvasive option remains popular with patients despite URS’s better outcomes

Lisette Hilton | UT CORRESPONDENT

National Report—Once considered a primary option for kidney stone treatment, shock wave lithotripsy (SWL) appears to be losing traction. Many urologists say its outcomes aren’t as reliable as those from ureteroscopy.

But others say it remains an option that works well with proper patient selection and technique and offers what ureteroscopy doesn’t: a noninvasive option. About three-fourths of respondents to an online Urology Times poll said they don’t think it’s time to retire SWL.

Timothy D. Averch, MD, said he was part of “lively” discussion on the topic at an AUA plenary session 2 years ago.

“I said that I don’t believe SWL is dead. I believe it’s going through a rough time; I would probably use the word ‘endangered.’ It’s going through a period of modification,” said Dr. Averch, who is professor and vice chair for quality and director of endourology at the University of Pittsburgh Medical Center.

SWL and ureteroscopy are competitive technologies that are often targeted at the same stone burden, according to Brian R. Matlaga, MD, MPH, professor of urology at Johns Hopkins Medical Institutions in Baltimore.

“The great difficulty with SWL is we have a limited ability to predict treatment outcomes,” Dr. Matlaga said. “The great attraction of SWL is that...”

Utility of PCa markers in African-Americans differs

Wayne Kuznar | UT CORRESPONDENT

San Francisco—Two urinary biomarkers for detection of prostate cancer have differing utility in African-American men undergoing prostate biopsy. Urinary PCA3 improved the ability to predict the presence of any and high-grade prostate cancer in this group, whereas the TMPRSS2:ERG urinary assay did not add significantly to standard detection and risk stratification tools, reported Jonathan L. Silberstein, MD, at the Genitourinary Cancers Symposium in San Francisco.

These urinary biomarkers had been validated previously in Caucasian men. “There was very little data before this study to demonstrate that urinary biomarker tests had any utility in African-American men,” said Dr. Silberstein, chief of urologic oncology at Tulane Cancer Center, New Orleans. “I would say that this study shows that not only are they of value in African-Americans, but it’s really important that we understand how limited traditional serum PSA and free PSA are in this patient population. As a result, some of these novel biomarkers, in particular PCA3, may have a real important role for this patient population.”

Dr. Silberstein and colleagues collected urine...
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ConfirmMDx is the Most Significant Independent Predictor for Prostate Cancer Detection on Repeat Biopsy\(^1\)\(^,\)\(^2\)

**DOCUMENT** Results: Multivariate Analysis of Known Risk Factors and Assay Performance\(^1\)

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Referenced:
PCa biomarkers: Hope for at-risk men

African-American men are at a substantially greater risk of prostate cancer, with an incidence of 208.7 per 100,000 compared to 123.0 per 100,000 U.S. Caucasian men (CA Cancer J Clin, epub ahead of print, Feb. 22, 2016). African-American men also have a significantly higher risk of prostate cancer death, with a rate of 47.2 per 100,000 compared to 19.9 per 100,000 U.S. Caucasian men. These figures highlight the importance of optimizing early prostate cancer detection in the African-American population.

Several new biomarkers are commercially available to aid in prostate biopsy decisions. These include blood tests such as the 4Kscore and Prostate Health Index (phi), which studies consistently show to be more specific than total PSA for clinically significant prostate cancer (Eur Urol 2015; 68:464-70; J Urol 2015; 193:1163-9). The PCA3 urine test is another commercially available marker that can be used to aid in repeat prostate biopsy decisions.

Comparative studies from Europe have shown that the 4Kscore and phi perform similarly to predict biopsy outcome (Eur Urol 2015; 68:139-46), and that phi outperforms PCA3 for the identification of clinically significant disease (Prostate 2015; 75:103-11). In fact, one of the key drawbacks of using PCA3 in clinical practice is the conflicting data on its relationship with aggressive disease. What we need most are markers that selectively identify significant cancers, in order to reduce unnecessary biopsies and over-diagnosis.

Less is known about the comparative performance of these new markers in the African-American population. A recent study confirmed that phi predicts aggressive pathology in African-American men (Urology, epub ahead of print, Dec. 10, 2015). Meanwhile, new data presented at the 2016 Genitourinary Cancers Symposium by Feibus et al suggest that PCA3 added to the prediction of high-grade disease in African-American men, but not in Caucasian men (see article, page 6). These findings may help to explain the mixed performance of PCA3 in previous studies and highlight the importance of evaluating new markers in ethnically heterogeneous populations.

Hopefully, the availability of new markers with improved performance in this population can help to enhance the diagnostic paradigm for African-American men in the future.

Stacy Loeb, MD, MSc

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BLOG

Out-of-control drug pricing requires creative solutions

Urologists have direct experience with drug shortages and their impact on pricing, thanks to the recent shortage of BCG. A sudden hike in the price of a competing generic drug seemed to be no coincidence, Henry Rosevear, MD, writes. He ponders a few similar, troubling cases and some proposed solutions.

READ DR. ROSEVEAR’S POST AT: urologytimes.com/drug-pricing

BLOG

Mentors: For many, the quest begins at home

When choosing to pursue a medical career and a particular specialty, mentors often play an influential role. For many, the quest to find a role model begins at home, says new UT blogger Nirmish Singla, MD, a urology resident and the son of a veteran urologist. “Without the giants before us, urology would not be where it is today,” he writes.

urologytimes.com/mentors

VIDEO

Treatment of OAB may reduce fall risk in elderly

Overactive bladder (OAB) and falls often carry a substantial burden for patients and society, and new research from the University of Pennsylvania suggests that treating OAB may lower fall risk. In this article and video, lead author Ravishankar Jayadevappa, PhD, discusses the findings and their clinical implications.

urologytimes.com/fall-risk

UT FOLLOWER OF THE MONTH

@DrCardonaGrau

Diana Cardona-Grau, MD, Albany Medical Center resident, is the Urology Times Twitter follower of the month! To be featured in this section, engage with us. TWITTER.COM/urologytimes

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Dr. Rosevear

FEBRUARY’S QUESTION OF THE MONTH

Would you favor a single-payer health care system?

NOT SURE 9%

NO 42%

YES 49%

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Enzalutamide maintains QoL longer than older agent

AR antagonist shows longer survival benefit in CRPC

Wayne Kuznar
UT CORRESPONDENT

Lille, France—Enzalutamide (XTANDI) is associated with longer progression-free survival, a higher response rate, and a greater benefit on health-related quality of life compared with bicalutamide (Casodex) in men with metastatic castration-resistant prostate cancer (mCRPC).

These findings were part of the phase II TERRAIN study, which was originally presented at the 2015 AUA annual meeting in New Orleans. Final results from the study were published in *Lancet Oncology* (2016; 17:153-63).

In related news, in men with non-metastatic or metastatic castration-resistant prostate cancer, a similar phase II trial known as STRIVE demonstrated a statistically significant increase in progression-free survival (PFS) for enzalutamide compared with bicalutamide (Hazard Ratio=0.24; 95% Confidence Interval, 0.18-0.32; p<0.001). Findings from STRIVE were recently published online in the *Journal of Clinical Oncology* (Jan. 25, 2016).

In the TERRAIN trial, enzalutamide extended PFS by almost 10 months compared with bicalutamide, said co-author Arnauld Villers, MD, professor of urology at the University of Lille, Lille, France.

Enzalutamide blocks androgen-receptor (AR) signaling and inhibits multiple steps in the AR pathway. It also has direct anti-tumor effects and has anti-proliferative and pro-apoptotic properties. In the pre- and post-chemotherapy settings, it improved overall survival and radiographic PFS compared with placebo in men with mCRPC.

Bicalutamide is used in combination with luteinizing hormone-releasing hormone (LHRH) analogue therapy for the treatment of metastatic prostate cancer. In a preclinical study, enzalutamide demonstrated superiority over bicalutamide on the AR signaling pathway.

Patients enrolled in TERRAIN had asymptomatic or mildly symptomatic mCRPC that had progressed despite treatment with an LHRH analogue or following surgical castration.

Please see ENZALUTAMIDE, on page 7

Study author: PCA3 ‘has real clinical value’

continued from page 1

following digital rectal examination (DRE) in 304 men, 182 of whom were African-American, without known prostate cancer prior to biopsy. PCA3 and TMPRSS2:ERG RNA copies were quantified using transcription-mediated amplification assays.

Prediction models for prostate cancer and high-grade prostate cancer were created using standard of care variables (age, race, family history of prostate cancer, prior prostate biopsy and abnormal DRE) plus PSA. Biomarkers of PCA3 and TMPRSS2:ERG were added to determine whether they increase the models’ performance compared with the base model. The final model constructed combined standard of care variables and PSA with both of the biomarkers.

Some 139 of the 304 patients (46%) were diagnosed with prostate cancer. PCA3 and TMPRSS2:ERG scores were greater in men with prostate cancer than in those without. The median PCA3 scores were 52.81 in those with versus 34.98 in those without prostate cancer, and the median TMPRSS2:ERG scores were 3.42 and 6.88, respectively. Men with prostate cancer more often had three or more cores, ≥33.3% cores, >50% involvement of greatest biopsy core, and Epstein-significant prostate cancer (p<0.01).

PCA3 added to the standard of care variables plus PSA model improved prediction for the detection of any prostate cancer in the overall cohort (0.747 vs. 0.677; p<0.001), in African-American men only (0.711 vs. 0.638; p=0.002), and in non-African-American men (0.781 vs. 0.732; p=0.0016).

PCA3 also added to the model for the prediction of high-grade (>Gleason 6) prostate cancer for the overall cohort (0.804 vs. 0.78; p=0.002) and the African-American subset only (0.759 vs. 0.717; p=0.003) but not in the non-African-American subset.

Decision curve analysis demonstrated significant net benefit with the addition of PCA3 compared with standard of care variables plus PSA.

**TMPRSS2:ERG doesn't improve concordance**

For African-American men, TMPRSS2:ERG did not improve concordance statistics for the detection of any or high-grade prostate cancer.

“Novel biomarkers should not be across-the-board tests,” Dr. Silberstein said. “I don’t think they’re of tremendous value to use routinely in every patient. But when you have discordant information—for example, if the biopsies are continuing to show me low-risk prostate cancer but the MRIs show an aggressive lesion—then I really think you need additional information to help you sort it through.”

“Our study demonstrates that for many African-American patients, PCA3 can help diagnose prostate cancer and particularly higher grade lesions,” he added. “So when I see an African-American patient who is reluctant to have a prostate biopsy, or had a previously negative biopsy with a persistently elevated PSA, PCA3 has real clinical value. Additionally, if I have a patient with significant comorbidities and a marginally elevated PSA who is unlikely to benefit from the diagnosis of a low-grade tumor, PCA3 in an African-American can influence my decision to biopsy.”

Dr. Silberstein has received honoraria from and served as a consultant/adviser to Astellas Pharma and Meditation. Two of his co-authors have disclosed relationships with several pharmaceutical and/or device companies. UT
Enzalutamide superior on PFS in all subgroups
continued from page 6

tion. The 375 patients enrolled were random-
ized to enzalutamide, 160 mg/day, or bicalu-
tamide, 50 mg/day.
To be eligible, patients had to have at least
two bone lesions or soft tissue disease, progres-
sive disease, ongoing LHRH analogue therapy
or surgical castration, and life expectancy of at
least 1 year.

“Half of the patients in the
enzalutamide arm reached
a >90% decrease in PSA by
month 6.”
ARNAULD VILLERS, MD

At baseline, median PSA levels were 20.6
ng/mL and 21.4 ng/mL in the enzalutamide
and bicalutamide groups, respectively. About
one-third of patients had bone and soft tissue
disease; about half had bone disease only. The
median baseline Functional Assessment of Can-
cer Therapy-Prostate (FACT-P) total score was
120 in the enzalutamide group and 122 in the
bicalutamide group.

Higher median PFS with enzalutamide

Median PFS, the primary endpoint, was 15.7
months in the enzalutamide arm compared
with 5.8 months in the bicalutamide arm, corre-
responding to a hazard ratio (HR) of 0.44
(p <.0001).

“The separation between the two curves was
seen early, at 3 months,” said Dr. Villers.
Enzalutamide was superior to bicalutamide
on PFS in all subgroups examined, based on
age, geographic location, performance status,
total Gleason score at diagnosis, disease charac-
teristics, PSA level, and use of LHRH analogue
or orchiectomy after metastasis.

By 13 weeks, the percentages of patients who
had a PSA response (decrease ≥50%) were 82%
in the enzalutamide arm and 21% in the bicalu-
tamide arm, and the percentage with a PSA
decrease ≥90% was 56% in the enzalutamide arm
versus 5% in the bicalutamide arm.

“Half of the patients in the
enzalutamide arm reached
a >90% decrease in PSA by
month 6,” he said.

There were differences
in favor of enzalutamide
on the Functional Assess-
ment of Cancer Therapy
(FACT)-General and the
FACT-P questionnaire
(p <.05). Enzalutamide was
also significantly superior
to bicalutamide on five of
seven health-related quality
of life domains (p <.05).

“Quality of life was
maintained for a signifi-
cantly longer time in the
enzalutamide group,” said
Dr. Villers.

Exposure to enzalutu-
amide was double that com-
pared with bicalutamide—
a median of 11.7 months
versus 5.8 months, respec-
tively. The rates of serious
adverse events were 31%
in the enzalutamide arm
compared with 23% in the
bicalutamide arm. Grade >3 adverse events
occurred in 40% of the enzalutamide arm and
38% of the bicalutamide arm. There were three
seizures overall: two in the enzalutamide arm
and one in the bicalutamide arm.

Astellas Pharma, Inc. and Medivation, Inc.
provided funding for the TERRAIN and
STRIVE studies. Dr. Villers is a consultan-
adviser for Astellas. Several of his co-authors
are consultants/advisers for or have another
relationship with Astellas Pharma and/or Medi-
vation.
For the treatment of adult men with Peyronie’s disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy

It’s time to see Peyronie’s disease differently. The only FDA-approved, nonsurgical treatment: XIAFLEX

Important Safety Information

WARNING: CORPORAL RUPTURE (PENILE FRACTURE) OR OTHER SERIOUS PENILE INJURY IN THE TREATMENT OF PEYRONIE’S DISEASE

Corporal rupture (penile fracture) was reported as an adverse reaction in 5 of 1044 (0.5%) XIAFLEX-treated patients in clinical studies. In other XIAFLEX-treated patients (9 of 1044; 0.9%), a combination of penile ecchymoses or hematoma, sudden penile detumescence, and/or a penile “popping” sound or sensation was reported, and in these cases, a diagnosis of corporal rupture cannot be excluded. Severe penile hematoma was also reported as an adverse reaction in 39 of 1044 (3.7%) XIAFLEX-treated patients.

Signs or symptoms that may reflect serious penile injury should be promptly evaluated to assess for corporal rupture or severe penile hematoma which may require surgical intervention.

Because of the risks of corporal rupture or other serious penile injury, XIAFLEX is available for the treatment of Peyronie’s disease only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the XIAFLEX REMS Program.

- XIAFLEX is contraindicated in the treatment of Peyronie’s plaques that involve the penile urethra due to potential risk to this structure and in patients with a history of hypersensitivity to XIAFLEX or to collagenase used in any other therapeutic application or application method
- Injection of XIAFLEX into collagen-containing structures such as the corpora cavernosa of the penis may result in damage to those structures and possible injury such as corporal rupture (penile fracture). Therefore, XIAFLEX should be injected only into the Peyronie’s plaque and care should be taken to avoid injecting into the urethra, nerves, blood vessels, corpora cavernosa or other collagen-containing structures of the penis

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In the double-blind, placebo-controlled portions of the clinical trials in Peyronie’s disease, a greater proportion of XIAFLEX-treated patients (4%) compared to placebo-treated patients (1%) had localized pruritus after up to 4 treatment cycles (involving up to 8 XIAFLEX injection procedures). The incidence of XIAFLEX-associated pruritus was similar after each injection regardless of the number of injections administered.

Because XIAFLEX contains foreign proteins, severe allergic reactions to XIAFLEX can occur. Anaphylaxis was reported in a post-marketing clinical trial in one patient who had previous exposure to XIAFLEX for the treatment of Dupuytren’s contracture. Healthcare providers should be prepared to address severe allergic reactions following XIAFLEX injections. The safety of more than one treatment course of XIAFLEX is not known.

In the XIAFLEX controlled trials in Peyronie’s disease, 65.5% of XIAFLEX-treated patients developed penile hematoma, and 14.5% developed penile ecchymosis. Patients with abnormal coagulation (except for patients taking low-dose aspirin, eg, up to 150 mg per day) were excluded from participating in these studies. Therefore, the efficacy and safety of XIAFLEX in patients receiving anticoagulant medications (other than low-dose aspirin, eg, up to 150 mg per day) within 7 days prior to XIAFLEX administration is not known. In addition, it is recommended to avoid use of XIAFLEX in patients with coagulation disorders, including patients receiving concomitant anticoagulants (except for low-dose aspirin).

In the XIAFLEX clinical trials for Peyronie’s disease, the most frequently reported adverse drug reactions (≥25%) and at an incidence greater than placebo included: penile hematoma, penile swelling, and penile pain.

Please see Brief Summary of full Prescribing Information, including Boxed Warning, on adjacent pages.

Please visit XIAFLEX.com/ut
XIAFLEX® (collagenase clostridium histolyticum) for injection, for intramuscular use

Brief Summary of Prescribing Information

For complete information, see the full prescribing information for XIAFLEX.

WARNING: CORPoreal RUPTURE (Penile Fracture) or OTHER SERIOUS PENILE INJURY in the TREATMENT of Peyronie's Disease

CORPoreal RUPTURE (Penile Fracture) or OTHER SERIOUS PENILE INJURY in the TREATMENT of Peyronie's Disease

In XIAFLEX clinical studies, reports of penile "popping" sound or sensation were reported, and in these cases, a diagnosis of corporal rupture cannot be excluded. Severe penile hematoma was also reported as an adverse reaction in 39 of 104 (3.7%) XIAFLEX-treated patients. These patients were given up to 4 treatment cycles of XIAFLEX or placebo. In each case, two injections of XIAFLEX or injections of placebo were administered 1 to 3 days apart. A penile modeling procedure was performed at the site on the second injection day, and in these cases, a diagnosis of corporal rupture cannot be excluded. These patients were managed without surgical intervention, but the long-term consequences are unknown.

Clinical Studies Experience in Patients with Peyronie's Disease

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. Adverse reaction rates observed in the controlled and uncontrolled clinical studies of XIAFLEX in Peyronie's disease, 1044 patients received a total of 7466 XIAFLEX injections.

Corporal Rupture and Other Serious Penile Injury

Almost all patients develop anti-product antibodies (anti-AUX-I and anti-AUX-II) during therapy. Antibodies to AUX-I are usually binding and neutralizing, whereas antibodies to AUX-II are generally binding but not neutralizing. Neutralizing antibodies to AUX-I or AUX-II were found in 60% and 51.8%, respectively, of patients tested.

In patients treated for these two indications, there was no apparent correlation of antibody frequency, antibody titer, or neutralizing status to clinical response or adverse reactions. Since the antigenic components in XIAFLEX (AUX-I and AUX-II) have some sequence homology with human matrix metalloproteinases (MMPs), anti-product antibodies could theoretically interfere with human MMPs. In vitro studies showed no evidence of cross-reactivity between anti-drug antibody positive patient sera and a series of relevant MMPs. In addition, no clinical safety concerns related to the inhibition of endogenous MMPs have been observed. Immunogenicity assay results are highly dependent on the sensitivity and specificity of the assay used and may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of anti-AUX-I and anti-AUX-II antibodies to collagenase clostridium histolyticum with the incidence of antibodies to other products may be misleading.

DxUG ACTIONS

Anticardiolipin drugs: XIAFLEX should be used with caution in patients receiving concomitant anticardiolipins (except for low-dose aspirin) [see Warnings and Precautions].

USE IN SPECIFIC POPULATIONS

Pregnancy

Category B

There are no adequate and well-controlled studies of XIAFLEX in pregnant women. Because animal reproduction studies are not always predictive of human response, XIAFLEX should be used during pregnancy only if clearly needed.

Risk Summary

Based on animal data, XIAFLEX is not predicted to increase the risk for major developmental abnormalities in humans.

Human pharmacokinetic studies showed that XIAFLEX levels were not quantifiable in the systemic circulation following injection into a Dupuytren's cord. Low levels of XIAFLEX were quantifiable in the plasma of evaluable male subjects for up to 30 minutes following administration of XIAFLEX into the penile plaques of subjects with Peyronie's disease [see Clinical Pharmacology in the full prescribing information].

All patients develop anti-product antibodies (anti-AUX-I and anti-AUX-II) after treatment with XIAFLEX, and the clinical signficance of anti-product antibody formation on a developing fetus is not known [see Adverse Reactions].

Animal Data

Reproduction studies have been performed in rats with intraperitoneal exposures up to approximately 11 times the maximum recommended human dose (MRHD) of XIAFLEX on a mg/m2 basis, and have revealed no evidence of impaired fertility or harm to the fetus due to collagenase clostridium histolyticum.

Nursing Mothers

It is not known whether collagenase clostridium histolyticum is excreted in human milk. Because many drugs are excreted in human milk, nursing mothers should be cautioned about the potential for adverse effects in breastfed infants.

Pediatric Use

The safety and effectiveness of XIAFLEX in pediatric patients less than 18 years of age have not been established.

Geriatric Use

The safety and effectiveness of XIAFLEX in patients 65 years of age or older have not been established. Although some clinical experience suggests that age may be a factor influencing response, age should not be considered an exclusion criterion for the use of XIAFLEX, since there is no evidence of altered pharmacokinetics or pharmacodynamics when XIAFLEX is used in this patient population.

OVERDOSAGE

The effects of overdose of XIAFLEX are unknown. It is possible that multiple injections or accidental injection of XIAFLEX into an injection site (e.g., a tendon) may cause adverse events on the injection site). Supportive and symptomatic treatment are recommended in these circumstances.

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Revised 10/2014

XP-03627
Surveillance: Reclassification risk drops after 2 years

Findings could lead to greater intervals between biopsies in low-risk patients

Cheryl Guttman Krader
UT CONTRIBUTING EDITOR

Baltimore—New findings from the Johns Hopkins University School of Medicine in Baltimore should be useful to clinicians looking to counsel anxious prostate cancer patients who are undergoing active surveillance.

Analyses of data from the prospectively maintained Johns Hopkins Active Surveillance Study show that reclassification rates are not equally distributed across time or risk groups, researchers reported at the 2015 AUA annual meeting in New Orleans.

Their study, which was subsequently published in the Journal of Urology (2015; 193:1950-5), included data from 808 men enrolled since January 2005 who were compliant with all follow-up biopsies, of whom 257 were categorized as very low risk and 251 were low risk. Kaplan-Meier survival analysis with adjustments for covariates using a Cox proportional hazards model was done to estimate freedom from reclassification.

Reclassification risk highest 2 years post-Dx

The results showed the risk of reclassification, defined as either increase in grade or volume, was significantly higher in the low-risk men than in the very-low-risk subgroup (2.4-fold and 1.8-fold, respectively). In both cohorts, however, the lifetime risk declined exponentially, falling by 30% with each favorable biopsy in the low-risk subgroup and by 35% in the very-low-risk men.

“Even as their follow-up in active surveillance lengthens, men continue to be concerned about whether their next biopsy will show evidence of disease progression and if they may have lost the opportunity for cure due to earlier sampling error,” said senior author Mufaddal Mamawala, MBBS, MPH, biostatistician for the Johns Hopkins Active Surveillance Study.

“The findings in our study allow clinicians to provide patients with confident answers and to reassure men who are compliant in active surveillance that their lifetime risk for reclassification falls with each non-reclassifying biopsy.”

Dr. Mamawala told Urology Times that a model of risk using the study results indicates that the lifetime risk of reclassification falls to virtually 0 after men have undergone 10 to 12 non-reclassifying biopsies.

Presenting the research, Ridwan Alam stated that in addition to helping inform men about their reclassification risk, the findings might lead to a shift in the monitoring protocol for men in active surveillance with an increased interval between biopsies for men at lowest risk.

“We hope that in the future, the risk of reclassification may be incorporated with other factors into a risk calculator that can be used to determine how often men in active surveillance need to undergo biopsy,” said Alam, a medical student at Johns Hopkins.

Men in the Johns Hopkins active surveillance program are classified as very low risk if they meet all Epstein criteria. If they do not meet at least one of the Epstein criteria but meet all of the D’Amico criteria and have a Gleason score of 6, they are considered low risk.

Misclassification, not progression

The authors suggested that the high rates of reclassification during the first 2 years of active surveillance and the lack of difference in rates between the two study subgroups likely reflects initial misclassification of disease rather than progression.

“These men in active surveillance who are classified as very low risk or low risk all have Gleason 6 disease, and we know from previous research that true Gleason 6 prostate cancer is not likely to progress,” Alam said. “Therefore, it is likely that the ‘reclassification’ in these men is the result of picking up tumor that was missed earlier because of undersampling.”

Speaking during the discussion, co-author H. Ballentine Carter, MD, professor of urology and oncology at Johns Hopkins, noted that with the advent of magnetic resonance imaging and the ability to visualize anterior tumors, the rate of initial misclassification is expected to decline.

Outcomes

Novel metric may support quality initiatives

Post-prostatectomy outcomes: Wide variability seen

Cheryl Guttman Krader
UT CONTRIBUTING EDITOR

Ann Arbor, MI—Developers of a novel metric for evaluating outcomes after radical prostatectomy are excited about its utility as a tool for supporting quality improvement initiatives for optimizing patient recovery after the procedure.

Known as NOTES (Notable Outcomes and Trackable Events after Surgery), the composite measure was created by members of the Michigan Urological Surgery Improvement Collaborative (MUSIC). MUSIC is a statewide, physician-led quality improvement program that is managed by the Coordinating Center housed at the University of Michigan, Ann Arbor and sponsored by Blue Cross Blue Shield of Michigan. NOTES captures eight variables chosen to represent outcomes consistent with uncomplicated surgery and early recovery:

- no rectal injury
- estimated blood loss ≤400 mL (90th percentile)
- length of stay ≤2 days
- drain placement ≤2 days
- catheter placement ≤16 days
- no indwelling catheter replacement
- no 30-day readmission
- no 30-day mortality

The tool and findings from a first-time analysis of collected data were presented at the 2015 AUA annual meeting in New Orleans.

“We considered feedback from post-RP patients invaluable for helping to identify criteria that would define a smooth and uncomplicated recovery after surgery.”

JAMES DUPREE, MD

AUA annual meeting in New Orleans.

“We believe NOTES will allow comparisons between diverse urological practices and help us to hone in on and identify quality improve-

Please see POST-RP OUTCOMES, page 12
Remote video visits associated with lower costs

Telehealth yields efficiency equivalent to office visits

Chase Doyle
UT CORRESPONDENT

Rochester, MN—Telemedicine may provide the answer to costly consultations. According to data from a recent study, remote video visits demonstrated equivalent efficiency and satisfaction when compared with traditional office visits for men with surgically treated prostate cancer.

“Video visits preserve efficiency and quality of care. They reduce patient costs, and they are a viable alternative to traditional health care delivery models,” said Boyd Viers, MD, a urologist at Mayo Clinic in Rochester, MN.

As Dr. Viers explained, recent studies have shown that disparities in access to health care lead to worse urologic outcomes. For patients in geographic areas with a lack of urologists, the implementation of telemedicine may provide a practical solution. However, limited data defining the role of telemedicine within urology exist.

“We currently have some data around telemounting, telemonitoring and telesurgery, and teleconsultation but nothing directly looking at the utility of remote telemedicine visits,” he said.

In a randomized, controlled trial powered to assess for equivalence in timing efficiency, Dr. Viers and colleagues enrolled 55 patients following radical prostatectomy. Video visits were given to patients at home and office visits followed the standard pathway. Invitation was offered to patients within 30 days of their pre-existing scheduled appointment. Patients living outside the states of Minnesota or Wisconsin and those who needed physical examination or failed to meet the technical requirements were excluded from the study.

The authors measured visit efficiency through direct observation. Satisfaction (of the patient and physician) and costs (for the patient) were assessed through a 21-point questionnaire, administered immediately following the visit.

“When we looked at our primary outcome—Please see TELEHEALTH, page 14

Program ‘empowers surgeons to improve quality’ continued from page 11

...ment opportunities that can be targeted with interventions for improving outcomes.”

“Recognizing the limitations of data from claims sources and traditional chart review for tracking outcomes, the elements of NOTES were chosen based on the general principles that the collected data would be unambiguous, accurate, meaningful, and actionable,” said first author Stacie Myers, BS, research assistant in urology at the University of Michigan and MUSIC database coordinator.

The NOTES criteria were developed by a statewide consensus panel of expert urologists and were endorsed by MUSIC Patient Advocates.

“We considered feedback from post-RP patients invaluable for helping to identify criteria that would define a smooth and uncomplicated recovery after surgery,” said James Dupree, MD, assistant professor of urology at the University of Michigan.

Speaking to Urology Times, senior author James E. Montie, MD, emphasized the reliability of the NOTES data points.

“It is important that the data be consistent and unambiguous so that they could be accurately extracted by data abstractors,” said Dr. Montie, MUSIC co-director and professor of urology, University of Michigan.

The first analysis of the NOTES data encompassed 1,570 radical prostatectomies performed in 33 MUSIC practices between April 2014 and March 2015.

Considering all patients, 21.7% of men experienced an event outside at least one of the criteria defining an uncomplicated NOTES pathway and 7.5% had two or more such deviations.

The most common deviations involved the drain placement (12.6%) and length of stay (8.1%) criteria. Rectal injury (0.5%) and mortality (0.3%) deviations were least common.

Deviations for the current criteria were assessed through a 21-point questionnaire, administered immediately following the visit.

“This is a process in evolution, and as we go forward and collect more data, the urologists in MUSIC will be involved in the process of deciding whether there is any need to revise the current criteria.”

JAMES E. MONTIE, MD

Opportunities for quality improvement

“The finding of significant variation among the MUSIC practices suggests there are opportunities for quality improvement that ultimately will improve the surgical care received in Michigan by men with prostate cancer,” Myers said.

To enable interpretation and action on the data, a quarterly report is being generated and disseminated automatically to MUSIC members. The report summarizes the deviation rates for individual surgeons, their practices, and the entire collaborative and presents them for the current and previous quarters, enabling identification of progress trends. Risk adjustment for race, age, insurance status, body mass index, Charlson comorbidity index, PSA, prostate volume, pathologic Gleason score, and pathologic T stage allows for equitable comparisons to other practices.

“The limitations of claims data make it difficult for an individual surgeon or practice to determine how their patients are doing relative to others in the area, state, or nation. We think MUSIC NOTES addresses that issue and empowers surgeons to improve quality of care within their practices,” said Dr. Dupree.

In addition to the stated criteria, NOTES is collecting information on specific complications that can guide understanding on the underlying cause(s) for criteria deviations.

And, the eight NOTES criteria are not set in stone.

“This is a process in evolution, and as we go forward and collect more data, the urologists in MUSIC will be involved in the process of deciding whether there is any need to revise the current criteria,” said Dr. Montie.
Narrow Band Imaging (NBI) visualized more bladder cancer than WLI*

Now, there is an even more powerful way to visualize bladder cancer than traditional WLI. NBI is a patented Olympus visualization technology clinically proven to help physicians see up to 28% more Carcinoma In Situ (CIS). Just push the NBI button — it’s that simple. Call 1-800-848-9024 to learn more about NBI.

*Based on a weighted average, studies have shown that using NBI allows physicians to visualize lesion boundaries. NBI is not intended to replace histopathological sampling as a means of diagnosis.

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Reduced patient travel seen with remote visits

continued from page 12

timing and efficiency—you can see that there are essentially no significant differences in timing parameters. The total time of the visit, as well as total face-time, patient-staff face-time, and patient wait-time were the same. When we assessed patient satisfaction, there was no significant difference in quality, efficiency, confidentiality of the visit, ability to share sensitive or personal information, or patient education overall,” reported Dr. Viers, who presented the findings at the AUA annual meeting in New Orleans. Findings were subsequently published in European Urology (2015; 68:729-35).

Costs significantly reduced

While there was no change in efficiency or patient satisfaction, costs were significantly reduced. With video visits, patients traveled significantly less time (mean, 26.9 vs. 148.2 minutes, p<.0001) and distance (mean, 10.1 vs. 130 miles, p<.0001) compared with office visits. Productivity was positively impacted, as well.

“In most cases, patients had to take a day off of work to come out to the clinic,” said Dr. Viers, “but they didn’t miss any work with the video visit.”

Dr. Viers estimated the cost of an office visit at $70. Video visits, on the other hand, cost approximately $1.

According to Dr. Viers, there was also a high level of provider satisfaction.

“Providers were very happy with the experience,” he said, “and our survey indicates that 96% of video-visitors would participate again.”

Although Dr. Viers believes video visits are applicable to current care pathways, he acknowledges financial and regulatory barriers, as well as cultural resistance, to the implementation of telemedicine services.

“Our solutions would be to offer video visits greater than 30 days from any scheduled appointment to allow patients the appropriate accommodations and to provide patient education regarding potential equivalence between the video visits and traditional office visits. We also need to have more focused legislative efforts addressing these issues,” he concluded. [1]

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**Urethroplasty rarely offered for anterior urethral stricture**

Most patients treated without undergoing prior imaging

**Wayne Kuznar**

UT CORRESPONDENT

Irvine, CA—Most men with anterior urethral strictures are treated without imaging, and 90% are not being offered urethroplasty. This despite the recommendation by the Société Internationale d’Urologie (SIU)/International Consultation on Urological Diseases (ICUD) that urethral reconstruction be considered a primary management option for men with bulbar urethral strictures, and also for strictures that are recurrent or refractory to a second internal urethrotomy (IU)/dilation.

The findings come from Joel Gelman, MD, director of the Center for Reconstructive Urology at the University of California, Irvine. The prospective data collection of men who were previously evaluated and/or treated for anterior urethral stricture were presented by Justin J. De Grado, MD, MS, fellow in male reconstructive urology at UC Irvine, at the 2015 AUA annual meeting in New Orleans.

With success rates up to 98% reported for urethroplasty in men with anterior urethral strictures, “it’s surprising that 90% of men are never offered urethroplasty to begin with,” Dr. De Grado said.

Data collected on 103 adult men who were seen between April 2011 and January 2014 were analyzed for the study. Disease-related information, outside imaging, treatments, and whether the patient was imaged and/or offered urethroplasty prior to treatment were evaluated. If the men could not recall whether they had been offered urethroplasty, but their records documented that they were offered it, they were counted as having been offered it as a treatment option.

Seventy-four of the 103 men were 31 to 70 years of age. More than half (55) had bulbar urethral strictures, 17 had panurethral strictures, and 20 had strictures in multiple locations.

Of the 103 men, 91 had prior treatment.

**Urethroplasty offered to nine patients**

“Only nine were offered urethroplasty, seven of which elected to undergo other treatments for personal choice, but 82 out of the 91 were never offered urethroplasty prior to being treated,” said Dr. De Grado.

Seventy-six of the 91 patients (84%) did not have urethral imaging before being treated. Of the 76 who did not have imaging performed, 51 had an IU, with 43 of them undergoing multiple procedures, and only 10 of the 43 underwent subsequent imaging after one or more failures.

Of the 25 who had dilation performed, 15 had multiple procedures, and only three of the 15 had subsequent imaging after one or more failures.

When combined, “that’s only 22% of men who underwent subsequent imaging after one or more failures,” he said.

“This is a problem,” Dr. De Grado said. “The reason this is a problem is because there’s a disconnect between the literature and practice patterns that we’re seeing in our general urology colleagues.”

SIU/ICUD contends that IU and dilation are recurrent or refractory to a second internal urethrotomy (IU)/dilation.

“Providers were very happy with the experience,” he said, “and our survey indicates that 96% of video-visitors would participate again.”

Although Dr. Viers believes video visits are applicable to current care pathways, he acknowledges financial and regulatory barriers, as well as cultural resistance, to the implementation of telemedicine services.

“Our solutions would be to offer video visits greater than 30 days from any scheduled appointment to allow patients the appropriate accommodations and to provide patient education regarding potential equivalence between the video visits and traditional office visits. We also need to have more focused legislative efforts addressing these issues,” he concluded. [1]
In men with mCRPC who progressed on ADT

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.
Every day tells a story.

Final analysis of the pivotal phase 3 trial.*

In men with mCRPC who progressed on ADT, consider ZYTIGA® (abiraterone acetate) first.

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 confirmatory (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.

II 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.\(^1\)

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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).

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INDICATIONS AND USAGE
ZYTIGA® (abiraterone acetate) Tablets
Brief Summary of Prescribing Information.

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, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess
ZYTIGA may cause hypertension, hypokalemia, 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 hypokalemia in 4% of patients, and grade 3 to 4 edema in 1% of patients treated with ZYTIGA [see Adverse Reactions].

Hypertension:
Co-administration of a corticosteroid suppresses adrenocorticotropin 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, hypokalemia 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 II or III heart failure (in Study 1) or NYHA Class II to IV heart failure (in Study 2) was not evaluated because these patients were excluded from these randomized clinical trials [see Clinical Studies (14) in full Prescribing Information]. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with ZYTIGA.

Adrenocortical Insufficiency:
Adrenocortical 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 function test abnormalities 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, Hypokalemia, and Fluid Retention due to Mineralocorticoid Excess [see Warnings and Precautions].
• Adrenocortical Insufficiency [see Warnings and Precautions].
• Hepatotoxicity [see Warnings and Precautions].

ADVERSE REACTIONS
ZYTIGA® (abiraterone acetate) Tablets
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 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, urinary 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, hypertriglyceridemia, hypo phosphatemia, elevated ALT and hypokalemia.

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>%</td>
<td>%</td>
</tr>
<tr>
<td>Musculoskeletal 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>17.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>6.1</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</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>Cardiovascular 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 Osteoarticular pain, Arthritis, Arthralgia, Joint swelling, and Joint stiffness
3 Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Myalgias
4 Includes terms Muscle pain, Subcutaneous myalgia, Myalgia
5 Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema
6 Includes all fractures with the exception of pathologic fracture
7 Includes terms Arthralgia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atriовentricular block complete, Conduction disorder, and Bradyarrhythmia
8 Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia
ZYTIGA® (abiraterone acetate) Tablets

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 in Study 1

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Abiraterone (N=791) Grade 3-4 (%)</th>
<th>Placebo (N=394) Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertriglyceridemia</td>
<td>62.5</td>
<td>53.0</td>
</tr>
<tr>
<td>High AST</td>
<td>30.6</td>
<td>36.3</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>28.3</td>
<td>19.8</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>23.8</td>
<td>15.7</td>
</tr>
<tr>
<td>High ALT</td>
<td>11.1</td>
<td>10.4</td>
</tr>
<tr>
<td>High Total Bilirubin</td>
<td>6.6</td>
<td>4.6</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>Abiraterone 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>Groin pain</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>0.9</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>Cough</td>
<td>17.3</td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>11.8</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>Contusion</td>
<td>13.3</td>
</tr>
<tr>
<td></td>
<td>Falls</td>
<td>5.9</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>Rash</td>
<td>8.1</td>
</tr>
</tbody>
</table>

1 Adverse events graded according to CTCAE version 3.0
2 Includes terms Edema peripheral, Pitting edema, and Generalized edema
3 Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness

ZYTIGA® (abiraterone acetate) Tablets

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Abiraterone (N=542) Grade 3-4 (%)</th>
<th>Placebo (N=540) Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<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>

1 Based on non-fasting blood draws

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 arm and 3 deaths in the placebo arms. There were 7 (0.5%) deaths due to cardiopulmonary 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.

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.

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 abiraterone was given together with a single dose of 1,000 mg abiraterone acetate. In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone (CYP2C8 substrate) was increased by 46% when pioglitazone was co-administered, increase the ZYTIGA dosing.

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

Pregnancy: Pregnancy Category X [see Contraindications]. ZYTIGA can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. While there are no adequate and well-controlled studies with ZYTIGA in pregnant women and ZYTIGA is not indicated for use in women, it is important to know that maternal use of a CYP17 inhibitor could affect development of the fetus. Abiraterone acetate caused developmental toxicity in pregnant rats at exposures that were lower than in patients receiving the recommended dose. ZYTIGA is contraindicated in women who are or may become pregnant while receiving 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 ZYTIGA.

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 body weight 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.

Nursing Mothers: ZYTIGA is not indicated for use in women. It is not known if abiraterone acetate 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 ZYTIGA, 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 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 after a single oral 1,000 mg dose of ZYTIGA 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 7-fold and the fraction of free drug increased 2-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.

Patients should be advised 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 ZYTIGA.

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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.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

• Patients should be informed that ZYTIGA and prednisone are used together and that they should not interrupt or stop either of these medications without consulting their physician.

• Patients receiving GnRH agonists should be informed that they need to maintain this treatment during the course of treatment with ZYTIGA and prednisone.

• Patients should be informed that ZYTIGA should not be taken with food and that no food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. They should be informed that the tablets should be swallowed whole with water without crushing or chewing. Patients should be informed that taking ZYTIGA with food causes increased exposure and this may result in adverse reactions.

• Patients should be informed that ZYTIGA is taken once daily and prednisone is taken twice daily according to their physician’s instructions.

• Patients should be informed that in the event of a missed daily dose of ZYTIGA or prednisone, they should take their normal dose the following day. If more than one daily dose is skipped, patients should be told to inform their physician.

• Patients should be apprised of the common side effects associated with ZYTIGA, including peripheral edema, hypokalemia, hypertension, elevated liver function tests, and urinary tract infection. Direct the patient to a complete list of adverse reactions in PATIENT INFORMATION.

• Patients should be advised that their liver function will be monitored using blood tests.

• Patients should be informed that ZYTIGA may harm a developing fetus; thus, women who are pregnant or women who may be pregnant should not handle ZYTIGA without protection, e.g., gloves. Patients should also be informed that it is not known whether abiraterone or its metabolites are present in semen and they should use a condom if having sex with a pregnant woman. The patient should use a condom and another effective method of birth control if he is having sex with a woman of child-bearing potential. These measures are required during and for one week after treatment with ZYTIGA.

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Urethroplasty increasingly favored for treating strictures
Academic affiliation among factors associated with performing procedure

Chase Doyle
UT CORRESPONDENT

Chicago—Although endoscopic management of male stricture is more commonly performed than urethroplasty, the ratio of these procedures is decreasing over time, particularly among newly certifying urologists. According to a study presented at the 2015 AUA annual meeting in New Orleans and subsequently published in *Urology* (2015; 86:830–4), urologists in 2012 were 3.4 times more likely to choose urethroplasty than in 2004.

“A changing paradigm in urethral stricture management favoring urethroplasty is evident over the last decade in the United States, both among urologists with more recent training as well as over time,” said lead study author Joceline S. Liu, MD, a urology resident at Feinberg School of Medicine, Northwestern University, Chicago. “Academic affiliation and proximity to a reconstructive fellowship program were also associated with performing urethroplasty.”

While endoscopic management of adult male urethral stricture has been widely utilized since its induction, according to Dr. Liu, recent data reflect poor long-term success rates for urethroplasty (25%) and dilation (60%) compared to open urethroplasty (over 90%). However, despite increasing evidence supporting urethroplasty, endoscopic treatment remains more common.

Using case log data of certifying and recertifying urologists (2003 to 2013) from the American Board of Urology, Dr. Liu, working with Christopher M. Gonzalez, MD, MBA, and co-authors, pulled only those cases specifying urethral dilation, direct vision internal urethrotomy (DVIU), or urethroplasty and graft harvest in males ≥18 years of age.

Among 6,320 urologists logging at least one reconstructive urology procedure, the researchers identified 95,747 urethral dilations (86.2%), 10,986 DVIU (10.0%), and 4,349 urethroplasties (3.9%).

The authors then looked for surgeon characteristics and surgeon-specific variables associated with different practice patterns.

“Over time,” said Dr. Liu, “we saw a significant change in practice patterns. According to the dataset, urologists were 2.5 times more likely to do a urethroplasty in 2013 than in 2003.”

Breaking down the data by certification stage, the authors found that new certification correlated with a decrease in ratio of dilation/DVIU to urethroplasty (*p*<.001). The ratio of dilation/DVIU to urethroplasty for new certification was much lower (7.9 to 1) compared to first (24.4 to 1), second (63.3 to 1), and third recertification cycles (99.5 to 1), wherein urethroplasty was increasingly rare (*p*<.001). Overall, newly certifying urologists performed urethroplasty 4.5 times more often than those recertifying.

“The ‘young bucks’ are doing urethroplasties far more often than those who are 40 years into practice,” said Dr. Liu. “Even though their volume might not be the same as the older [doctors], the proportions of urethroplasties to DVIU are extremely different. I thought there might be a trend, but I did not expect to see it to that degree.”

Academics more likely to perform urethroplasty
Urologists with academic affiliation were eight times more likely to perform urethroplasty than non-academically affiliated urologists (*p*<.001). The data also showed geographic discrepancies: all states with a genitourinary reconstructive surgery fellowship maintained a ratio of 10.5 to 1 or less.

According to Dr. Liu, the majority of urethroplasty cases are performed by a small number of urologists with high volume, academic affiliation, recent residency graduation, and residence in a state with a reconstructive urology fellowship.

Although Dr. Liu would not pinpoint a single cause for the change in practice, she suggested that contemporary training and familiarity with urethroplasty may be contributing to this paradigm shift.

“It’d be really nice to take the concepts of this study and include multi-institutional groups to look at true data,” Dr. Liu concluded, “looking at practice patterns but also looking retrospectively at all of their patient demographics. The problem is that at an academic institution it’s really hard to capture what community urologists are doing. I think that’s something we still need to figure out.”

Imaging ‘should absolutely be performed’
continued from page 14

have equal efficacy, and may be offered as a reasonable first option for single, short bulbar strictures as they are outpatient procedures with minimal recovery time, despite a much lower long-term success rate. A repeat procedure can be indicated “as long as the recurrence happens late,” he said. A third IU/dilation is generally not recommended.

These recommendations are based on findings that IU has a higher stricture-free rate when strictures are short (<1 cm), when it’s a first attempt, when performed on a single stricture rather than multiple strictures, and when the stricture is located in the bulbar urethra.

However, more recent data from Santucci and Eisenberg show a much lower success rate of IU on a first attempt, “and it rapidly approaches 0% on multiple attempts,” Dr. De Grado said.

“The majority of men are never being imaged and they’re being diagnosed only with cystoscopy, which can really only give you the appearance of the urethra distal to the stricture, the caliber of the distal aspect, and the approximate location,” said Dr. De Grado. “We really need to know the length, the number of the strictures, and we need to know the exact location, which only urethral imaging can provide. Urethral imaging should absolutely be performed if we’re to adequately counsel our patients on their best options.”

Further, urethroplasty should always be offered, even as a primary treatment option, given its high success rate, and should definitely be offered with prior failure of IU.
Sexual Dysfunction

Increase in plaque injection frequency seen

Study: Minority of urologists treat Peyronie’s disease

Benjamin P. Saylor
CONTENT MANAGING EDITOR

Chicago—Peyronie’s disease (PD) is surgically treated by a minority of urologists, and urologists who subspecialize in andrology perform a disproportionate number of procedures to treat the condition.

Those were among the findings of a case log analysis that was presented at the 2015 AUA annual meeting in New Orleans and subsequently published in Urology (2016; 87:205-9).

Despite Peyronie’s disease being a common condition (affecting an estimated 3% to 9% of men), there is a relative absence of evidence-based outcome studies of PD, impeding the development of treatment pathways regarding its management, until recently with the introduction of the new AUA guidelines, said first author Daniel T. Oberlin, MD, urology resident at Northwestern University Feinberg School of Medicine, Chicago. As a result, practice patterns regarding Peyronie’s disease treatment vary widely.

Dr. Oberlin and his co-authors sought to review contemporary surgical trends in the treatment of Peyronie’s, looking at changes in practice patterns, surgeon-specific characteristics, treatment selection, practice characteristics and geography, and specialty training. For their review, they utilized American Board of Urology case logs from 2004-2013. Cases were identified using CPT codes 54200 (Injection procedure for Peyronie’s disease); 54110, 54111, and 54112 (Excision of plaque [and grafting]); and 54360 (Correction of angulation without plaque excision [plication]). Penile prosthesis surgery was excluded from review.

The logs encompassed a total of 6,564 urologists. The authors found that 8,195 surgical procedures were recorded for the treatment of Peyronie’s disease over the 10-year period reviewed.

Few urologists treat PD surgically

The authors found that during the period covered in their analysis, only 15.4% of urologists treated Peyronie’s disease surgically. They also found that 5.3% of urologists in the cohort were self-reported andrologists, and that they performed 18.5% of all Peyronie’s procedures. Non-andrologists performed an average of 6.8 procedures per year, compared with 28 procedures per year for andrologists (p=0.001).

The authors also compared plaque injection with surgical correction.

“We found that the frequency of plaque injection increased annually, from 499 procedures in 2004 to almost double that in 2013, whereas the rate of surgical correction remained fairly stable,” reported Dr. Oberlin, who worked on the study with Christopher M. Gonzalez, MD, MBA, and co-authors. Injection therapy accounted for 82% of all procedures, which Dr. Oberlin said was unexpected because “prior to 2013, few studies found a significant benefit to injection therapies. Of note, all cases were performed prior to the introduction of collagenase clostridium histolyticum (Xiaflex), the first FDA-approved injectable for the treatment of PD.”

Evaluating surgical corrections, 73% were performed without plaque excision. 21% were performed with excisions of plaque ≤5 cm in length, and 6.2% were performed with excisions of plaque >5 cm. The authors also reported a 31.3% increase in the performance of plication compared to plaque excision and grafting. The rate of plication increased with an equal decline in the use of plaque excision.

Commenting on his group’s findings, Dr. Oberlin said, “With the introduction of the AUA guidelines on the treatment of Peyronie’s disease, urologists now have access to an excellent framework for the standardized evaluation and treatment for PD not previously available.”

“In our study, we found a minority of urologists are performing surgery for PD, and this coincides with previous reports that many urologists may manage PD conservatively or refer patients to urology colleagues who specialize in its treatment. This was demonstrated by the finding that urologists who subspecialized in andrology perform a disproportionate number of these procedures, and we hypothesize that many urologists may prefer only medical treatment approaches, or refer their patients to a urologist who treats PD more commonly,” Dr. Oberlin said.

One of Dr. Oberlin’s co-authors is a consultant for American Medical Systems, Coloplast, and GlaxoSmithKline.

TTrials: Experts react to long-awaited research

Raising testosterone shows benefits in men 65 years of age and older

Lisette Hilton
UT CORRESPONDENT

Philadelphia—In the largest randomized, controlled trial to investigate the benefits of testosterone therapy in men 65 years of age and older, researchers report raising testosterone concentrations offers moderate benefits in sexual function and some benefit on mood and depressive symptoms.

The New England Journal of Medicine published results of three of seven of the Testosterone Trials (TTrials) (2016; 374:611-24). The TTrials are a coordinated group of seven studies testing the effect of a testosterone gel compared with a placebo gel. The New England Journal study includes the results of the three primary trials, which examined sexual function, physical function, and vitality.

Urologists interviewed by Urology Times said the research provides clear evidence of testosterone therapy’s benefits, while one endocrinologist, who called the study very well...
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Results ‘seal the deal’ on T’s benefits in men

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designed, said its results suggest testosterone therapy is over-prescribed.
Study authors, led by Peter J. Snyder, MD, professor of medicine at the University of Pennsylvania Perelman School of Medicine in Philadelphia, studied 790 men 65 years of age and older. Subjects, who had serum testosterone concentrations of less than 275 ng/dL and symptoms suggesting hypoandrogenism, received either testosterone gel or placebo gel for 1 year.

“The results of the TTrials show for the first time that testosterone treatment of older men who have unequivocally low testosterone levels does have some benefit. However, decisions about testosterone treatment for these men also will depend on the results of the other four trials—cognitive function, bone, cardiovascular, and amenia—and the risks of testosterone treatment,” Dr. Snyder said in a Penn press release.

The TTrials were supported by a grant from the National Institutes of Health’s National Institute on Aging.

T boosts sexual activity, mood
Results from the three trials include:
- Testosterone treatment increased serum testosterone levels to the mid-normal range for men 19 to 40 years of age.
- Increased testosterone levels were associated with significantly improved sexual activity, sexual desire, and erectile function.
- While 6-minute walking distance did not differ significantly between groups in the Physical Function Trial, it did when researchers looked at data from all three trials, with the testosterone group improving significantly more (20.5% vs. 12.6% in the placebo group).
- Men receiving testosterone therapy reported slightly improved mood and lower depression severity than those on placebo. But testosterone did not appear to impact vitality.
- Finally, heart attack, stroke, other cardiovascular events, and prostate conditions were similar in men who received testosterone and those who received placebo. The authors note, however, the number of men in the TTrials was too small and length of trials too short to draw conclusions about the risk of testosterone treatment.

Urologists share reactions
Reaction from experts Urology Times spoke with was largely positive, although one thought leader pointed out that the use of testosterone therapy was short term, as was follow-up.

“Although there was already level 1 evidence that T therapy improved sexual desire and erection quality, as well as reducing fat mass and increasing lean mass, these results ‘seal the deal’ that T therapy has significant benefits for men, including mood and physical activity,” said Abraham Morgentaler, MD, director of Men’s Health Boston and assistant clinical professor of urology at Harvard Medical School, and Beth Israel Deaconess Medical Center, Boston.

“Whereas testosterone critics have attempted to undermine the benefits of T therapy by claiming that prior studies were too small, or of poor quality, or unduly influenced by pharmaceutical funding, this multicenter, NIH-funded study eliminates those concerns. In the face of these results, it can no longer be claimed that the benefits of testosterone therapy are unproven,’” Urology Times Editorial Council member Arthur L. Burnett, II, MD, MBA, also praised the study.

“This is a solid study with respect to its well-defined study population, high-caliber study design, rigor, and execution, and excellent choice of endpoints. It affirms the understanding that testosterone therapy (in the form of topical therapy administered to eugonadal therapeutic levels) significantly benefits sexual function (sexual activity, sexual desire, and erectile function) and modestly improves physical function and depressive symptoms,” said Dr. Burnett, professor of urology at Johns Hopkins University, Baltimore.

Dr. Burnett included a caveat with his comments.

“These positive conclusions must be tempered, however, by the constraints of this study that enrolled fairly healthy older but not elderly men and the relatively short-term use of therapy (and 12 months) and follow-up (12 months),” he said.

Ranjith Ramasamy, MD, director of male reproductive medicine and surgery and assistant professor of urology at the University of Miami, told Urology Times these are important findings, statistically and clinically.

“The results are significant because the results of the study are in contrast to the results of the TEAM trial (JAMA 2015; 314:570-81) and because this is the first randomized trial that showed beneficial effects in elderly men who received testosterone therapy,” Dr. Ramasamy said.

Discussing the trials with UT, Ajay K. Nangia, MBBS, says urologists have been caught in the crosshairs of patients who want to be treated for symptoms, a lack of solid research, bad media coverage, and the FDA’s announcement that testosterone would be considered off-label except for treatment of specific medical conditions.

“This is like giving women HRT after menopause. The Women’s Health Initiative left that a complete mess about whether to use it or not. The pendulum went one way, then the other way; now, it’s back, trickling to the middle. So, I hope that will happen with testosterone. It was not used a lot in the ‘80s and ‘90s. After 2000, the use of testosterone increased very dramatically,” said Dr. Nangia, professor of urology at the University of Kansas Medical Center, Kansas City.

“Then, all of the sudden, the FDA came down on us like a brick after the cardiovascular papers and adding cardiovascular risk to the label, and we’ve gone the other way,” he added. “I hope these trials bring us back to the mean and at least allow us to use it appropriately with short-term (and I hope one day long-term) evidence.”

Endocrinologist Rebecca Z. Sokol, MD, MPH, professor of obstetrics and gynecology and medicine at the Keck School of Medicine of the University of Southern California, Los Angeles, called the paper “a very well-designed study.”

“I would have been interested to know how many increased sexual events actually took place. The difficulty of these studies is not being able to recruit enough men to adequately analyze risks of treatment,” Dr. Sokol told Urology Times.

Findings suggest over-prescription
The study is revealing when it comes to prescription of testosterone, according to Dr. Sokol.

“The most important finding in this study is that 51,085 men were screened, but only 14.7% met the low testosterone level inclusion criteria. It is true that men spent $2 billion on testosterone prescriptions last year, that indicates that many more men are using testosterone than there are men with low testosterone levels, suggesting it is over-prescribed,” Dr. Sokol said.

AbbVie provided funding as well as testosterone gel and placebo gel for the study. Dr. Snyder receives consulting fees from Watson Laboratories, and several of his co-authors have a financial or other relationship with one or more pharmaceutical companies. Dr. Ramasamy is a consultant to Beckman Coulter, and Dr. Morgentaler has received research grants and/or lecture honoraria and/or has been a consultant for AbbVie, Antares Pharma, Bayer, Clarus Therapeutics, Endo, Eli Lilly and Co., and Pfizer. UT
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Epigenetics and genetics: The future of cost-effective care?

New tools, including DTC tests, have wide-ranging clinical and medicolegal ramifications

James M. Hotaling, MD, MS  ●  Douglas T. Carrell, PhD

Genetics and epigenetics will likely become a valuable asset in urologic care. The central dogma of biology is that DNA can lead to RNA production, which can make proteins, alterations of which can cause disease states. This paradigm has been further revealed by improved understanding of dynamic epigenetic pathways wherein changes and exposures over the course of an individual’s lifetime can cause noncoding changes that alter gene expression and protein production.

Epigenetic marks may be driven by DNA sequence, alterations in various enzymes, or environmental exposures, such as diet, exercise, and other medical conditions that fluctuate over the course of a lifetime change in the gene expression. Perhaps even more intriguing is that these acquired changes can be passed on to future generations through a man’s sperm (Nature Neuroscience 2014; 17:89–96) (figure 1). The impact of lifestyle and exposure to a man’s spermatogonial stem cells and propagation of these changes to offspring through methylation has been proven in many studies.

This article will provide a clear understanding of the basis for the genetic and epigenetic tools that are increasingly used in medicine, highlight some of these tools currently used in urology, and explain the clinical and medicolegal ramifications of direct-to-consumer tests.

The genetic revolution: Urologic applications

While the genome-wide association studies (GWAS) have yet to live up to their full potential, whole genome sequencing costs have fallen from about $2.7 billion for the human genome project to $3,000 to $5,000. This has stimulated the growth and development of the Precision Medicine Initiative, whereby genetic data can not only aid in diagnosis, but also improve therapy through a better understanding of the utility of therapeutic options based on genotype.

Currently, many GWAS studies are limited to oncology. While these have led to the development of clinically relevant prognostic tests such as GenomeDx, 4K score, Prolaris, Oncotype DX (Genomic Prostate Score), and...
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1. Roehrborn, 2015 Urology Practice, 2-Year L.I.F.T. Study Results

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ConfirmMDx, they are only the tip of the iceberg. All of these tests rely on genetic, RNA, or epigenetic data to help stratify and prognosticate prostate cancer risk.

In order to fully understand these tests, one must first examine how genetic studies are performed. Typically, blood, saliva, or tissue undergoes either whole genome or targeted genetic sequencing to identify single nucleotide polymorphisms (SNPs), which are variations in a cytosine, guanine, adenine, or thymine at one specific location in the genome.

If we think of the genome as a library of books, these are changes of letters on individual pages of a book. To extend the analogy further, we would say that we have three copies of the same book and on page 52, line 8, word 6, one book has “THE” (patient 1), another (patient 2) has “TEH,” and another (patient 3) has “HET.” Each book can be thought of as an individual. When we compare tens of thousands of individual people, these changes can be associated with a phenotype of interest, such as male infertility (figure 2). What makes these studies difficult is that thousands of genes may contribute to a phenotype such as prostate cancer, and the disease state may be the result of one gene or SNP of high penetrance or the combination of multiple SNPs.

Although most of this work has been done in urologic oncology, in large part through access to large registries such as Surveillance, Epidemiology, and End Results (SEER), other investigators are now working on developing applications to benign urologic diseases. Work by the DCCT/EDIC group (funded by the National Institute of Diabetes and Digestive and Kidney Diseases) has identified genetic factors that increase the risk of men with type 1 diabetes developing erectile dysfunction (J Urol 2012; 188:514-20).

Our hypothesis has been that genetic changes that predispose a man to ED, once identified, will be able to prognosticate treatment response for ED, thus saving millions in wasted clinic visits and phosphodiesterase type-5 inhibitor trials. Work such as this will help to further solidify the role of genetic screening and testing in urologic disease. Ultimately, urologists may be able to rely on the validated results of a genetic test to guide targeted interventions.

Epigenetics: Case study in sperm methylome

While genetic analysis evaluates changes to the coding of DNA, epigenetics involves noncoding, heritable changes that affect gene expression. Epigenetic factors include methylation changes to cytosine bases of DNA, chemical modifications to histones that bind DNA in nucleosomes and microRNAs. DNA methylation and certain histone modifications cause structural changes that impede access to transcription factors of a gene, thus inhibiting transcription and protein synthesis, while other histone modifications facilitate access of transcription factors to genes in that region of the genome. Epigenetic regulation can be very specific in “turning on” or “turning off” gene expression and can be inherited through the germline (figure 3).

To understand the role of epigenetics, we will use male infertility as an example to highlight the potential of using epigenetic information in clinical practice. Currently available tests for male reproduction have poor prognostic ability in defining fertility (N Engl J Med 2001; 345:1388-93). Semen analyses have up to 400% inter-test variability, and the only finding that absolutely precludes natural pregnancy is azoospermia.

Recent work has demonstrated that multiple semen analyses from the same individual do not improve upon the predictive ability of a single semen analysis (Hum Reprod 2014; 29:1360-7). However, recent studies have demonstrated that sperm DNA methylation at specific genes may provide better prognostic value in not only predicting fecundity, but also predicting the probability of normal embryogenesis in couples undergoing in vitro fertilization. A panel of methylation marks was able to classify male fertility status with 82% sensitivity and a positive predictive value of 94% (Fertil Steril 2015; 104:1388-97). Tests such as this will likely make
Phase III: Bladder [NCT02450331]—“IMvigor 010”

A Phase III study of atezolizumab (MPDL3280A) treatment versus observation as adjuvant therapy in patients with PD-L1–positive, high-risk muscle-invasive bladder cancer (MIBC) after cystectomy.

**Study Endpoints**

**Primary Outcome Measure:**
- Disease-free survival

**Secondary Outcome Measures:**
- Overall survival
- Disease-specific survival
- Distant metastasis-free survival
- Number of patients with adverse events
- Percentage of anti-therapeutic antibody response to atezolizumab (MPDL3280A)
- Atezolizumab maximum serum concentration
- Score of participant-reported health status in EuroQoL 5-Dimension, 5-Level Version Questionnaire

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Trial consistent with information on ClinicalTrials.gov as of November 17, 2015. These compounds and/or uses are investigational and have not been approved by the US Food and Drug Administration. Efficacy and safety have not been established. The information presented should not be construed as a recommendation for use.
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their way into the diagnostic armamentarium of andrology, as well as other areas of urologic care.

Epigenetic marks, unlike an individual’s DNA sequence, are not immutable and change over the course of the lifespan in response to environmental or biological cues. Therefore, they allow a dynamic insight into the response of an intervention, such as starting a medication, as well as the effects of lifestyle factors. For example, it has recently been shown that aging alters the epigenetic marks in sperm at some genes associated with neuropsychiatric disorders, which are well known to increase in offspring of men with advanced paternal age. As the costs of these tests continue to decrease, it is very likely that they will become a routine part of clinical care.

One scenario where they will likely be used is in assessing the risk and speed of disease progression. For example, if a woman with overactive bladder was being seen for an initial clinical workup, she could undergo a methylation-based screening test from a urine sample. This would be able to prognosticate which treatment she would respond to, how her disease would progress, and whether a surgical intervention should be deployed as first-line therapy. Currently, AUA guidelines depict a logical stepwise approach of interventions from least to most invasive. Genetics and methylation could potentially help inform this progression.

Currently available genetics tests
The Human Genome Project has enabled companies to perform direct-to-consumer genetic testing; examples include Counsyl, Natera, 23andMe, and Ancestry.com. Counsyl and Natera perform prenatal testing and require a physician’s order to perform. Counsyl screens for a panel of 100 autosomal recessive diseases such as cystic fibrosis in order to determine a couple’s chances of having an affected child. Natera offers cancer screening as well as preimplantation genetic testing: screening of cryopreserved embryos to ensure that they do not carry a genetic disease present in one or both parents with the objective being to transfer only unaffected embryos.

23andMe and Ancestry.com offer direct-to-consumer genetic testing that has no FDA approval for clinical diagnosis beyond determining the carrier status for traits such as cystic fibrosis (23andMe). Ancestry.com uses DNA to determine ethnicity. It is crucial for clinicians to understand the limitations of these tests. Although Ancestry.com and 23andMe can provide some genetic information, any of their markers must be verified by a clinical diagnostic genetic test.

Thus, no clinical diagnostic or therapeutic interventions should be undertaken solely on the results of these tests. All of these patients should see a genetic counselor and undergo appropriate genetic testing from a certified laboratory.

The future
Recent studies have shown that single gene and microarray methods of genetic analysis have limited utility in diagnosing the causes of many diseases due to the rarity of many disease-causing SNPs and due to the increased understanding that many SNPs of importance may reside outside of the coding region (exons) of a gene. Whole genome analysis has become a realistic option, both in price and the feasibility of analytical and database tools needed for whole genome sequencing and interpretation of the data. The potential of real utility in the clinical decision making suggests that the era of precision medicine has begun and will continue to become more routine and powerful in the next 10 years (Cell Tissue Res 2016; 363:295-312). It is likely that cost-effective medicine will necessitate whole genome sequencing as a routine part of medical care that will facilitate a better understanding of optimal pharmacotherapy and other treatments.

The use of epigenetic analysis in clinical medicine is also advancing and holds promise in both diagnostics and in monitoring aging, lifestyle, and other risks. Sperm epigenetic analysis may provide prospective parents with information about the risk of advanced age, lifestyle choices, and other factors on the health of a future child.

Recent advances in gene editing using novel methodologies, especially the CRISPR/Cas system, have finally moved forward the realistic possibility of gene therapy to cure certain genetic anomalies. Clinical trials are beginning, and it is likely that this area will rapidly evolve soon. While current methodologies are most advanced for genetic therapy, epigenetic editing methodologies will likely evolve in the near future.

Sources: James Hotaling, MD, MS, and Douglas T. Carroll, PhD
“I’ve talked to patients who say they’ve chosen a surgeon based on the Scorecard. Patients are much more technologically savvy; they think the answer to all their questions can be found online. But with surgeon quality, we don’t have the metrics. We’re trying to compare surgeons whose practices are completely different. Patients don’t understand that.”

Mark Garzotto, MD
Portland, OR

“T he database ProPublica used doesn’t have the information to account for all the factors that are important if you’re going to compare surgeon to surgeon. They were limited in terms of the quantity and the quality of information that can be extracted from the Medicare database. It’s easy for the public to go to that site and walk away with either a positive or negative impression that isn’t based on scientific research.

Mark Garzotto, MD
Portland, OR

“I haven’t felt any impact from the Surgeon Scorecard. There are various ratings from Medicare or insurance companies or surveys, but never have I had a patient go on a Centers for Medicare & Medicaid Services site, or other sites, to check out complication rates. That information should be submitted to CMS, and as chairman of surgery at our hospital, as we’re looking at credentialing and re-credentialing, we look at complication rates. But even for us, the problems are: One, are all complications reported? And two, the definition of complication is not standardized. You can have a pimple or a full-blown infection, and they are simply reported as complications. What’s a readmission? Are patients re-admitted because they’re sick and septic, or are they just being readmitted because the hospital doesn’t have an observation unit, which isn’t considered an official readmission for assessing complication rates?

It’s hard to make sense of it, but patients will be looking at it, so it’s something we’re going to need to be aware of.”

V. Michael Bivins, MD
Homewood, AL

“I’ve been doing prostatectomies for over 1,000, but when I looked at my numbers, it only cited 20-some cases. So if the volume doesn’t seem to be accurate, my main concern would be whether the rest of the information on complication rates is actually accurate.

No one asks me about the Scorecard specifically. Most of these inaccuracies I find on the Internet are debunked by the practitioner who knows my reputation or my outcomes based on their other patients who have been through my office. That usually suffices in giving patients confidence that what they saw was not necessarily accurate.”

Joseph Renzulli, II, MD
Providence, RI

“W hile the database ProPublica used doesn’t have the information to account for all the factors that are important if you’re going to compare surgeon to surgeon. They were limited in terms of the quantity and the quality of information that can be extracted from the Medicare database. It’s easy for the public to go to that site and walk away with either a positive or negative impression that isn’t based on scientific research.

I’ve talked to patients who say they’ve chosen a surgeon based on the Scorecard. Patients are much more technologically savvy; they think the answer to all their questions can be found online. But with surgeon quality, we don’t have the metrics. We’re trying to compare surgeons whose practices are completely different. Patients don’t understand that.”

Mark Garzotto, MD
Portland, OR
Appropriate patient selection key in SWL

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it’s a noninvasive modality.”

Two things are working against SWL in today’s treatment of kidney stones, according to Dr. Averch. One is a culture favoring a more conservative approach and allowing stones to pass. The second is widespread access to complex ureteroscopy.

“Patient preference a consideration

It’s hard to discount something that’s popular among patients.

A lot of patients like the noninvasive nature of SWL—especially after they hear they might need a ureteral stent following ureteroscopy, according to Ojas Shah, MD, professor of urology and director of endourology and stone disease, Columbia University Medical Center, New York.

“But then when you discuss the success rates of the procedures with the patient—including stone-free rate—the overall success rate of ureteroscopy is higher, so a lot of patients end up choosing ureteroscopy,” Dr. Shah said.

Dr. Matlaga agreed patients prefer the concept of noninvasive versus minimally invasive.

“Conceptually, most of us would rather not have foreign objects going inside our bodies, if given that choice. But the concession might come with counseling of the patient about outcomes,” Dr. Matlaga said.

The good news is that counseling has gotten better. Today’s urologists are smarter about which patients will succeed with SWL, according to Dr. Averch.

“So, instead of using it as sort of a shotgun approach for all stones, we’ve now defined the population much, much better for those that will have success,” Dr. Averch said. “By identify-

The best stone location for SWL is the upper pole of the kidney, the renal pelvis, or upper ureter, he said.

The second factor is stone density.

“If you know the stone is made from a harder material, like calcium oxalate monohydrate, you typically don’t want to do SWL because that stone is more dense. If it’s made from cystine, you don’t want to do SWL because it will not break up the molecular bonds of that particular stone,” he said.

Urologists can measure stone density on a computed tomography scan. And if the Hounsfield unit measures less than 1,000, the literature suggests patients will have a better outcome with SWL. If it’s greater than 1,000, the chances of a good outcome with SWL are less, Dr. Averch said.

The third factor is skin-to-stone distance.

“If the patient’s stone is beyond the reach of the shock wave focal point, it’s going to fail. We know from the literature that a distance of 10 cm will decrease the success of SWL. Now, that is modifiable based on the particular shock wave machine you are using, but, regardless, if you get too far away, your success rate is going to go down,” Dr. Averch said.

Using all these parameters leaves urologists with a small population of patients who are good candidates for SWL, according to Dr. Averch.

Dr. Sankey, who has been practicing for nearly 3 decades and continues to see patients a few days each month, agreed that stones in the lower two-thirds of the ureter are best treated

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AUA releasing updated guidelines in San Diego

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by ureteroscopy. And he and his staff of urologists use basically the same parameters before recommending a preferred method of stone removal to patients.

What’s missing from the recommended parameters is patient preference, and that’s a big issue. Dr. Sankey said.

“Most of our panel [of doctors] would rather have two or three episodes of SWL rather than a long ureteroscopy (with the possibility of retained fragments) or two episodes of ureteroscopy,” Dr. Sankey said.

When patients are candidates for both procedures, each seems to offer benefits and drawbacks. In a study of 160 patients comparing objective outcomes with patient-reported outcomes after SWL and ureteroscopy for ureteral calculi, researchers found patients undergoing SWL had a stone-free rate of 61.5% after one session, 81% after two sessions, and 93.5% after three sessions versus 100% after ureteroscopy (World J Urol 2013; 31:1569-74). Complications were comparable, as was overall satisfaction between the groups. However, patient-reported outcomes for voiding symptom and time to return to routine activity were significantly better in the SWL group.

Optimizing SWL technique

Urologists that adhere to proper patient selection and evidence-based SWL technique will get good results with SWL, according to Dr. Sankey.

Among those best practices, Dr. Sankey’s practice published research more than a decade ago suggesting the use of general anesthetic versus intravenous sedation leads to better outcomes (J Urol 2002; 168:35-7). That’s because less stone movement results in better fragmentation.

“We think using low power to protect the kidney and then ramping up the power is valuable. We think a slow rate gives you better fragmentation,” Dr. Sankey said.

“All of these things have been published in the urologic literature. But a lot of centers that I’ve visited around the country don’t pay attention to the technique.”

The current technology of SWL has been shown to have better results with a slower rate, Dr. Shah agreed.

“There is data that changing the amount of energy that’s used can help break stone. And ramping up the SWL power, as opposed to using a single power all the way through the procedure, can help protect the kidneys and improve fragmentation,” Dr. Shah said.

Guidelines in the works

The AUA is in the process of redoing its surgical management guidelines and is expected to release those at the 2016 annual meeting in San Diego, according to Dr. Matlaga.

“Until those are rolled out, we’d say that patients with particularly large-volume stones (if you reference guidelines such as the AUA’s or the European Association of Urology’s)—from 1.5 to 2 cm in size—should not undergo SWL as a primary therapy because it’s too large a stone burden to expect complete fragmentation and expulsion of the fragments,” Dr. Matlaga said.

“For patients with ureteral stones, stones in the

Please see SWL, on page 30

Pros and cons of SWL and URS

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“Most of our panel [of doctors] would rather have two or three episodes of SWL rather than a long ureteroscopy (with the possibility of retained fragments) or two episodes of ureteroscopy.”

—NOEL SANKEY, MD

“More and more urologists are getting trained in complex ureteroscopy and are getting comfortable with it.”

—TIMOTHY D. AVERCH, MD

“The great difficulty with SWL is we have a limited ability to predict treatment outcomes.”

—BRIAN R. MATLAGA, MD, MPH

“Skill is important with both procedures, but more so with ureteroscopy.”

—NOEL SANKEY, MD
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Higher accuracy in predicting metastasis means better classification by risk and more appropriate levels of treatment.
URS undergoing changes in technology

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proximal ureter, guidelines suggest both shock wave and ureteroscopy are considered acceptable. For patients with distal ureteral stones, patients having ureteroscopy are more likely to get a better outcome, meaning the stones are out in a single procedure.”

From a guidelines standpoint, both SWL and ureteroscopy are acceptable treatment approaches for patients with uncomplicated kidney stones, according to Dr. Matlaga.

The future

Ureteroscopy is undergoing changes in its technology, including new digital options and miniaturized and disposable ureteroscopes.

The next paradigm in technology that non-invasively treats stones might be coming out of the University of Washington in Seattle, where researchers have demonstrated that a technology they developed using ultrasound moves stones within the kidney. (For more about this, see www.urologytimes.com/Ultrasound-stones.)

“They’ve demonstrated the ability to take a stone that fragments in the lower pole and move it out of the lower pole and into the ureter,” Dr. Averch said. “[In the future,] you may get a situation where you fragment a stone [with SWL regardless of location] and move it into the lower pole, then use this new technology to move the fragments out of the lower pole and to pass.”

Improvements in SWL technology have been minimal. Interestingly, the older-generation lithotripters are actually better than the newer-generation machines, according to Dr. Shah.

“The older machines had larger focal zones with much better shock wave penetration to the stone, so they pulverized and broke the stones much better. The newer shock wave lithotripters tend to have a tighter focal zone, which unfortunately do not break up stones as well and, potentially, increase your risk of complications, such as a hematoma,” Dr. Shah said.

Just how SWL will fare in the future continues to be up for debate, according to Dr. Shah. He said not only has ureteroscopy technology improved, but training for the procedure has, as well.

“Newer data in the U.S. and Canada shows ureteroscopy volumes have been going up, while SWL volumes have essentially been going down,” Dr. Shah said. (For more about this trend, see www.urologytimes.com/SWL-URS) “The newer urologists coming out of residencies and fellowships now are much more prone to doing ureteroscopy over SWL because they’ve been better trained in it and the success rates are higher.”

Dr. Shah is a scientific advisor, consultant and lecturer for Boston Scientific and special government employee for the FDA. Dr. Matlaga is a consultant for Boston Scientific, and Dr. Averch is a speaker for Bard Medical.

Stone incidence rising among adolescents, females

Benjamin P. Saylor
CONTENT MANAGING EDITOR

Philadelphia—Kidney stone incidence is increasing, particularly among adolescents, females, and African-Americans in the United States, according to findings from a recent study.

The research was published online in the Clinical Journal of the American Society of Nephrology (Jan. 14, 2016).

Findings raise concerns

First author Gregory E. Tasian, MD, MSc, MSCE, expressed concern over the findings and their implications.

“The emergence of kidney stones in children is particularly worrisome, because there is limited evidence on how to best treat children for this condition. The fact that stones were once rare and are now increasingly common could contribute to the inappropriate use of diagnostic tests such as CT scans for children with kidney stones, since health care providers historically have not been accustomed to evaluating and treating children with kidney stones,” Dr. Tasian, a pediatric urologist and epidemiologist at The Children’s Hospital of Philadelphia, said in a press release from that institution.

“These trends of increased frequency of kidney stones among adolescents, particularly females, are also concerning when you consider that kidney stones are associated with a higher risk of chronic kidney disease, cardiovascular, and bone disease, particularly among young women,” Dr. Tasian added.

The overall increase in kidney stones in children and adolescents is not a new trend, but the current study provides greater clarity on the specific groups of patients at greatest risk by analyzing age, race, and sex characteristics among children and adults in South Carolina over a 16-year period, from 1997 to 2012.

Risk doubles in children

Drawing on state medical records, the authors analyzed data from nearly 153,000 child and adult kidney stone patients from a total population of 4.6 million. Overall, the annual incidence of kidney stones increased 16% between 1997 and 2012. The greatest rates of increase were among adolescents (4.7% per year), females (3% per year), and African-Americans (2.9% per year). Between 1997 and 2012, the risk of kidney stones doubled during childhood for both boys and girls, while there was a 45% increase in the lifetime risk for women.

The highest rate of increase in kidney stones was among adolescent females, and in any given year, stones were more common among females than males aged 10 to 24 years. After age 25, kidney stones became more common among men.

Among African-Americans, the incidence of kidney stones increased 15% more than in Caucasians within each 5-year period covered by the study.

Possible factors for the rise in kidney stones may include poor water intake and dietary habits, such as an increase in sodium and a decrease in calcium intake. However, the current study did not examine dietary differences.

Dr. Tasian added that the age, sex, and race differences that his team found among kidney stone patients will require further study, but that the patterns they found may assist physicians and public health officials in designing targeted prevention strategies for people at higher risk for the condition.
COMING SOON

500 mg
FILM-COATED TABLETS
Is modifier –22 an option for multiple stones?

Documentation must indicate significantly more work was provided during procedure

Q I am under the impression that ureteroscopy (URS) simple is for a single stone. If I perform URS with the same scope (ie, rigid URS for two separate stones in ureter) and/or perform URS with combination of both rigid and flexible URS for stones in both the ureter and kidney (the flex would involve ureteral access sheath), are both by definition complex based on multiple stones? Let’s assume in this case that stones are all on the same side. If the stones are bilateral, I understand that is a separate bilateral code. My office manager believes complex is based on time, but my impression is that the complex modifier is based on work involved and that multiple stones on the same side should include a complex modifier on the bill.

A The way you have asked the question, we will assume that when referring to the “complex modifier,” you are talking about using modifier –22, defined as: “Increased Procedural Services: When the work required to provide a service is substantially greater than typically required, it may be identified by adding modifier –22 to the usual procedure code. Documentation must support the substantial additional work and the reason for the additional work (ie, increased intensity, time, technical difficulty of procedure, severity of patient’s condition, physical and mental effort required). Note: This modifier should not be appended to an E/M service.”

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.

However, before we get to discussion about the modifier –22, we will first restate the positions that are circulating about using modifier –22, defined as: “Increased Procedural Services: When the work required to provide a service is substantially greater than typically required, it may be identified by adding modifier –22 to the usual procedure code. Documentation must support the substantial additional work and the reason for the additional work (ie, increased intensity, time, technical difficulty of procedure, severity of patient’s condition, physical and mental effort required). Note: This modifier should not be appended to an E/M service.”

In the end, it is the provider who determines whether the complexity of the service truly warrants the use of the modifier –22, but it is the payer review that will determine whether the documentation supports substantially more extensive effort to increase the payment.

First, the shortened version of the AUA policy, according to the AUA Policy & Advocacy Brief article, “Modifier 59 or New Medicare Modifiers X[ESPU]: Which One Should I Use?” (Feb 17, 2015): “Multiple stones in the same structure (bladder, ureter and kidney) using the same procedure, should only be reported once. Stones in different structures (ureter and kidney, bladder and ureter) should be reported separately and an appropriate modifier 59 or more specific X modifier should be appended to the code if they are bundled within the NCCI [National Correct Coding Initiative] edits. With the exception of stones treated by ureteroscopy with lithotripsy and insertion of stent (CPT code 52356), insertion of an indwelling ureteral stent is separately reported.” To be sure you have a clear understanding, we want to emphasize that the AUA has decided that there are three separate structures in the urinary system: the kidney (which includes the pelvis of the kidney), the ureter, and the bladder.

We will, also, note that although the AUA opinion stated here will carry weight in the correct interpretation of the use of modifiers such as –59, –XS, and –XU that may be applicable to multiple stones, the AUA is not a payer and therefore the statement should be treated as a guideline and not a rule. We are all still waiting for Medicare to provide further instruction related to these modifiers.

We bring this up based on the second part of your question with regard to stones in both the ureter and kidney. Based on AUA interpretation, instead of considering using modifier –22 to report the ser-
separate structures. Assuming that you used lithotripsy to treat both stones and you left an indwelling stent at the conclusion of the services, the correct coding would be 52356 (Cystourethroscopy, with ureteroscopy and/or pyeloscopy; with lithotripsy including insertion of indwelling ureteral stent [eg, Gibbons or double-J type] and 52353-XS (Cystourethroscopy, with ureteroscopy and/or pyeloscopy; with lithotripsy [ureteral catheterization is included]).

Note: –59 can be used, but we encourage the more accurate –XS for most payers, including Medicare.

Regarding the first part of your question and getting back to the use of modifier –22 (complex modifier), we point you to the NCCI policy manual:

“Modifier 22: Modifier 22 is defined by the CPT Manual as ‘Increased Procedural Services.’ This modifier should not be reported routinely but only when the service(s) performed is (are) substantially more extensive than the usual service(s) included in the procedure described by the HCPCS/CPT code reported.

Occasionally a provider may perform two procedures that should not be reported together based on an NCCI PTP edit. If the edit allows use of NCCI-associated modifiers to bypass it and the clinical circumstances justify use of one of these modifiers, both services may be reported with the NCCI-associated modifier. However, if the NCCI PTP edit does not allow use of NCCI-associated modifiers to bypass it and the procedure qualifies as an unusual procedural service, the physician may report the column one HCPCS/CPT code of the NCCI PTP edit with modifier 22. The Carrier (A/B MAC processing practitioner service claims) may then evaluate the unusual procedural service to determine whether additional payment is justified.”

Based on this directive, the question then becomes: Is the work provided to treat the second stone significantly more work? Perhaps a better way to ask this question is: Does the documentation for the service substantiate the use of the modifier indicating that significantly more work was provided during the operative session? We refine the question back to documentation, as the use of modifier –22 will almost always kick the claim to manual review.

Considering that most reviewers are paid to review the claim with an eye toward denying the extra payment and the frame of reference of the reviewer is rarely that of an experienced surgeon for that service, the easiest way to indicate the work was in fact “substantially more extensive” is to include a relative time reference. In short, the documentation should include something that lets the reviewer know that the service required, for example, 140% of the time normally required to treat a single stone due to repositioning the scope after withdrawal and reinsertion of the scope.

In other words, although the complex modifier (modifier –22) is not literally time based, your office manager has a very good position in basing the use of the modifier on time due to the way claims are processed and reviewed. In the end, it is the provider who determines whether the complexity of the service truly warrants the use of the modifier –22, but it is the payer review that will determine whether the documentation supports substantially more extensive effort to increase the payment.

Q

Our urology group is currently discussing how to best calculate physician productivity and to devise a fair compensation plan (and vacation schedule). Do you do consulting work with groups? Can you recommend any resources that might be helpful as our group designs fair productivity/compensation guidelines?

A

Yes, we consult with groups to assist in schedule planning and in designing compensation packages. We have worked with many groups that were uncomfortable with their compensation package and wanted assistance with modification. As you are aware, there are many models for compensation within a practice from pure production (“eat what you kill”) to equal pay for all. In the end, there is no truly one-size-fits-all, and each system has issues that need to be addressed.

Balancing incentive for work, life balance for partners, offsets for administrative burden, and group health is important for new groups and for established groups.

The groups that have asked for assistance more often than others are those with compensation models on each end of the spectrum. On the pure productivity compensation end of the spectrum, we have seen problems with practices for which the system was developed when all partners were working full time and the model called for expenses to be split equally and paid by each partner out of the money that was collected for that provider. Changes in the practice that will create problems in this model include the addition of a new partner who is not as busy, a partner who is older and now working part time, the addition of a physician assistant, the addition of ancillaries, or even a renewed focus on billing services “incident to” the provider in the office.

One solution was to implement an expense payment formula that was based on actual production (CPT codes produced). There are other solutions for resolving this problem, but they are too numerous for this article. We have found over the years that any solution must take into account the current practice make-up, goals of the principals, and marketplace considerations at a minimum.

On the other end of the spectrum, a practice that splits revenue equally after expenses are paid regardless of work have come to us quite often with a complaint of unequal work for pay. Again, the solution is not always the same but usually involves some type of hybrid payment system based partially on production and partially on the production of the group as a whole.

We have always favored the hybrid approach, structured in a way that rewards production to a degree but also takes into account market pressures (serving Medicare and Medicaid population), production versus time issues (robotic service time relative to office-based production), overhead costs, etc. In short, balancing incentive for work, life balance for partners, offsets for administrative burden, and group health is important for new groups and for established groups. Any group that you elect to work with should not come in with a one-size-fits-all approach but should work with your group to establish a compensation system that fits the practice goals and personality.

We also addressed compensation issues in a March 12, 2013, Urology Practice Today article (bit.ly/Compensationtips).

Q

We are getting Medicare edits billing CPT 76942 with CPT 50200. The error message is that CPT 76942 is a component of CPT 50200. Can you explain?

A

If you enter the two codes into the bundling matrix of AUA Coding Today, you will see that 76942 (Ultrasonic guidance for needle placement [eg, biopsy, aspiration, injection, localization device], imaging supervision and interpretation) is included in 50200 (Renal biopsy; percutaneous, by trocar or needle).

76942 is bundled into 50200 and can be unbundled with a modifier if you can justify the use of the modifier—in other words, if the reason for the performance of the bundled procedure meets the definition of the modifier to be used. If the reason for performing the ultrasound guidance for needle placement is to perform the biopsy being charged, there is no modifier that can be justified. Unfortunately, you should only charge for the 50200.
For many years, urologists and other physicians have administered medications in an office setting under a system sometimes known as “buy and bill.” These treatments have historically been paid under the “medical benefit” of a health insurance plan, just like professional services and other office procedures. Examples include leuprolide (Lupron) injections for prostate cancer and bacillus Calmette–Guérin (TheraCys, TICE BCG) treatments for bladder cancer.

In an attempt to control the utilization and cost of these treatments, many insurers have begun to cover the drugs under the pharmacy benefit (with no payment to the physician unless they have an in-house pharmacy), and pay the administration fee under the medical benefit. Medicare (the Centers for Medicare & Medicaid Services) pays most prescription drugs under the Part D benefit, but generally reimburses medications administered by physicians under the Part B physician fee schedule.

In this article, I will describe some nuances of this “service line” that you should understand in your roles of small business owner and treatment provider, especially as it pertains to Medicare.

How buy and bill works

“Buy and bill” services typically include an administration charge (injection, infusion, instillation, implantation) and a separate drug charge. These treatments usually involve medicines that are expensive to acquire, cannot be self administered, may be subject to restrictions by the manufacturer, or have other constraints compared to a “prescription.” In 2004—as legislated by the Medicare Modernization Act of 2003 (http://bit.ly/MedModLaw)—reimbursement for drugs paid under Part B began to be linked to “average sales price” (ASP) reported by manufacturers to the government. Many regulations determine how ASP is reported and calculated (http://bit.ly/PartBASP, http://bit.ly/PartBregs), and CMS has issued several clarifications through rule making since the program began.

ASP is intended to reflect the acquisition cost for providers, and the basis for determining payments to physicians under Part B. ASP is updated quarterly (based on a 6-month lag), and Medicare payments to physicians are 106% of ASP, a markup intended to help defray the additional “overhead” in a practice: acquisition, storage, handling, loss, wastage, etc.

Six percent is a narrow margin to manage any business, but the absolute dollars determine which office-based medication administrations can be profitable versus unprofitable: 6% of $20 is very different than 6% of $10,000, and in any given practice it is the weighted average (volume X price) of all drugs that determines the profit/loss of the buy and bill business. This fact has prompted some to suggest that the ASP system encourages the use of more expensive drugs when lower cost alternatives are available (more on this later).

Other factors likely contribute to lowering the 6% margin significantly. First, ASP is an average based on national sales figures; assuming a normal distribution of actual acquisition costs around a mean, one half of physicians will at any given time be paying more than average for a drug and thus eating into the 6% margin. Second, reimbursement is based on ASP that was calculated two quarters earlier; assuming physicians purchase drugs

### The Bottom Line

**Robert A. Dowling, MD**

Dr. Dowling is vice president of medical affairs and policy for IntrinsiQ Specialty Solutions (an AmerisourceBergen Specialty Group company), a board-certified clinical informaticist, and the former medical director of a large metropolitan urology practice. He resides in Ft. Worth, TX.

The actual average reimbursement for the Medicare buy and bill service line is at most 104% of ASP, and for many practices some drugs are reimbursed at less than the acquisition cost.

### The actual average reimbursement for the Medicare buy and bill service line is at most 104% of ASP, and for many practices some drugs are reimbursed at less than the acquisition cost.

#### UT Table: Buy and bill: Calculating profit/loss

<table>
<thead>
<tr>
<th>Example</th>
<th>Amount provider paid for drug</th>
<th>Hidden price concessions (2%) in ASP calculation</th>
<th>Acquisition cost</th>
<th>ASP</th>
<th>ASP+6%</th>
<th>2% sequestration</th>
<th>Part B payment</th>
<th>Effective reimbursement rate</th>
<th>Profit/loss</th>
</tr>
</thead>
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<td>True market average</td>
<td>No</td>
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<td>100.00</td>
<td>106.00</td>
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<td>103.88</td>
<td>1.04</td>
<td>3.88</td>
</tr>
<tr>
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<td>100.00</td>
<td>98.00</td>
<td>103.88</td>
<td>2.08</td>
<td>101.80</td>
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<td>1.80</td>
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<td>2.12</td>
<td>103.88</td>
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<td>101.80</td>
<td>1.00</td>
<td>–0.20</td>
</tr>
</tbody>
</table>

Source: Robert A. Dowling, MD
to minimize shelf life, any price increases that occur in the interval between when the ASP was calculated and the drug was actually purchased, administered, and charged are borne by the practice and effectively not reimbursed.

Third, any price concessions granted by the manufacturer must be included in the ASP calculation; some of these concessions cannot be passed on to providers, thus effectively lowering ASP and in turn 106% of ASP. Finally, the 2% sequestration adjustment on Medicare reimbursement (http://bit.ly/Sequestrationreports) is applied to the entire fee, not just the 6% profit.

Taking all of these factors into account, the actual average reimbursement for the Medicare buy and bill service line is at most 104% of ASP, and for many practices some drugs are reimbursed at less than the acquisition cost (table). The additional administration fee (injection, for example) may offset this narrow profit/loss in some cases, but the services should be understood separately as they arguably have different costs and overhead. Wastage and missed billing are additional risks for this business.

An incentive to use high-cost alternatives?

Critics of the ASP methodology worry the reimbursement system may provide an incentive to use high-cost alternatives when there are legitimate therapeutic alternatives, thus driving up Part B spending on drugs. There is actually direct and indirect evidence to support an opposite conclusion—that the ASP methodology may incentivize low-cost drug utilization. According to the Medicare Payment Advisory Commission report in 2015 (http://bit.ly/MEDPACreports), prior to ASP, Part B drug spending was rising at an average of 25% per year; after ASP implementation, spending has only increased an average of 4.4% per year.

The ASP methodology may actually encourage use of low-cost alternatives as they enter the market, as the two-quarter lag in ASP calculation allows physicians to acquire these drugs at lower cost but under the same reimbursement (for two quarters); ie, at higher profit margin. Finally, two demonstration projects using a reimbursement scheme that removed any incentive for providers to use higher cost drugs revealed drug spending remained flat or actually increased (J Oncol Pract 2014; 10:294-7, J Oncol Pract 2014; 10:187-9).

These observations suggest the ASP methodology may have no influence or actually encourage use of lower cost alternatives; a possible explanation is that provider’s choice of alternatives is driven by the proportional financial risk they assume in buying, holding, and collecting coinsurance for the drug rather than the proportional benefit of the profit. If this is true, the ASP system may be making an important contribution to holding drug spending in check.

Bottom line: Urologists should understand their buy and bill service line in detail, especially the heavily regulated Medicare business. Rather than “making” money even on expensive drugs, nuances of the ASP methodology can significantly erode any opportunity for profit—or worse, result in loss. Examine each drug’s cost and reimbursement separately, track quarterly updates to ASP and fee schedules carefully, and consider calculating a weighted average to look at the business as a whole and by payer. Understanding this aspect of your practice will help as you encounter changes and reform to our systems of reimbursement.
Legislation renews IRA charity tax break

Qualified charitable contributions for IRA owners over age 70½ now permanent

Q I am 73 years old and still working, but have to take required minimum distributions from my individual retirement account. Can I make charitable donations from my IRA?

A The Protecting Americans from Tax Hikes Act of 2015 was signed into law on Dec. 18, 2015. The law renews a long list of tax breaks known as “extenders” that have been expiring on an annual basis. This legislation makes some of the rules effective through Dec. 31, 2016. Others are effective through 2019, and some are effective permanently.

Provisions in the Act also make changes to existing tax rules that were not part of the extenders. All of these changes will affect financial planning now and in future years.

If you’re over age 70½ and are required to take a minimum distribution from your IRA, you’ll again have the option to make that distribution tax free by directing it to the charity of your choice. President Obama has signed a legislative package that included making permanent “qualified charitable distributions” (QCDs). The provision for tax-free distributions from IRAs to charities is now permanent. This break allows qualifying IRA owners to make a qualified distribution of up to $100,000 from the IRA to a charity. The transfer counts as a required minimum distribution yet is excluded from your gross income.

These distributions can be a convenient way to support charitable causes and get a tax break while meeting tax requirements for IRAs. However, as with any change to the tax code, you must adhere to a number of criteria to ensure the tax savings. You should be well aware of the following:

• A QCD permits annual direct transfers to a qualified charity up to $100,000 that can be excluded from taxable income, but still count toward satisfying the Required Minimum Distribution (RMD).
• Funds distributed to the IRA owner first, no matter how briefly, then contributed to charity do not meet the criteria for a QCD.

Q How do bonds react to changes in interest rates?

A Bonds are issued by corporations or municipalities, which “promise” to pay you a predetermined amount of interest, typically on a semi-annual basis, plus return your principal to you on a specified maturity date. As an investor, you can choose to hold the bond until maturity or sell it prior to maturity through the municipal bond marketplace and receive proceeds based on the bond’s current value. This is known as “market risk.”

As interest rates rise, the value of an existing bond decreases, since it pays a fixed rate of interest lower than what is being offered in the market. On the other hand, bond values appreciate when interest rates decline. This inverse relationship means a bond’s market value is dependent on the number of years remaining until maturity. The longer the maturity time frame, the more sensitive the bond will be to interest rates.

Financial Tips

• The provision for tax-free distributions from IRAs to charities is now permanent, allowing qualifying IRA owners to make a qualified charitable distribution (QCD) of up to $100,000 from the IRA to a charity.
• Only IRA owners age 70½ and older can take advantage of making a QCD.
• Other factors that can affect a decision to make an IRA charitable distribution include whether your charitable contributions exceed your otherwise deductible limit and whether you itemize deductions.
• As interest rates rise, the value of an existing bond decreases. Bond values appreciate when interest rates decline.

QDs can be made from any IRA (including an annuity), but not from a simplified employee pension-IRA, SIMPLE (Savings Incentive Match Plan for Employees) IRA, or inherited IRA.

The QCD will be included in the distribution amount the IRA custodian reports on the Form 1099R. It’s up to the IRA owner or their tax preparer to report how much of the distribution went to charity.

Other factors that can affect a decision to make an IRA charitable distribution include whether your charitable contributions exceed your otherwise deductible limit, whether you itemize deductions, the potential loss of tax-deferred growth on the amount distributed from the IRA, and the effect on the size of future RMDs.

Send us your questions

Send your questions about estate planning, retirement, and investing to Joel M. Blau, CFP, c/o Urology Times, at UT@advanstar.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 advice.
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Groups urge increased focus on men’s health

Urologists, non-profits, key stakeholders unite in Washington

Washington—It was foggy and overcast on Sept. 25, 2000 in San Francisco. For 40 minutes, Kevin Hines, crying, paced back and forth on the Golden Gate Bridge high above the water, hoping that just one person would look at him and ask if something was wrong and could they help.

Nobody did.

Then, he found a spot on the bridge from which he would jump. He catapulted himself into the water, immediately realizing he had made the worst mistake of his life; that he didn’t want to die.

But, Hines told attendees at a White House Dialogue on Men’s Health meeting on Jan. 8, 2016, three miracles occurred that day.

First, a woman driving by saw him jump and called a friend in the Coast Guard. Soon after Hines surfaced after plunging into the water more than 70 feet deep below the surface, help arrived.

Second, as he was nearly drowned and broken from slamming into the water, a sea lion emerged beneath Hines, helping him stay on the surface until he could be rescued. And third, as he arrived at the hospital, a world-renowned neurosurgeon who just happened to stay an extra hour at work operated and fixed Hines’ broken back, preserving his ability to walk and run.

Today, Hines, who suffers from bipolar disorder, still contemplates suicide almost daily. But he has sought and received help and is now working on a new film, “Suicide: The Ripple Effect.”

“Four out of five suicides are male,” said Dr. Turek.

High-level stakeholders present

The White House conference brought together experts on men’s health from government, professional sports, nonprofit organizations, and health care, who together raised awareness of the need for increased focus on men’s health.

The event was organized by the Department of Health and Human Services in collaboration with Men’s Health Network (MHN) and Disruptive Women in Health Care. It drew more than 200 participants.

“If you want to take great care of men, you need to engage them, and to engage them, you need to listen.”

PAUL TUREK, MD

Assistant to the President and Cabinet Secretary Broderick Johnson joined U.S. Surgeon General Vivek Murthy, MD, MBA, to lead the discussion, which Dr. Turek said provided “hope… hope for boys, hope for men, hope for health care, hope that my vision is a shared one.”

The conference, he said, “was a charged environment. I’m not sure anything concrete came out of it, but it was probably the first time that stakeholders were present at such a high level of listening with federal officials. Having the surgeon general there… hopefully will lead to larger steps in the future toward making something concrete out of this initiative.”

“We were very pleased with this event and all of the excitement around advancing boys’ and men’s health,” said Brandon Leonard, director of strategic initiatives at MHN. “The stories and programs that were shared are truly inspiring, and we look forward to continuing this momentum with our federal government partners as well as all of the organizations represented and many more around the country who are dedicated to this important cause.”

MHN contends that lack of health care and overall lack of engagement among American men is contributing to a large-scale health deficit in the U.S. According to MHN, men have higher mortality rates for nine of the top 10 causes of death and die 5 years earlier than women, on average.

For the past several years, MHN has advocated establishment of an Office of Men’s Health within the federal government to coordinate health care services for men.

“That idea has been teetering, but it has never been realized,” said Dr. Turek. “It might just be that the Boy Scouts, the YMCA, urologists, non-profits, professors, sports teams getting together (such as at the White House conference) will push it over the hump. The sad fact is that men are being underserved, but this idea has never had this high level of support and overall grassroots interest.”

MHN: ACA fails to address men’s health

Last November, the MHN commented on a proposed Department of Health and Human Services rule on nondiscrimination within the Affordable Care Act (ACA), contending that the ACA fails to address serious health concerns affecting men.

MHN told HHS that males are being excluded from a number of health coverage benefits afforded to females by the ACA, including lack of access to preventive services, contraception, and sexual health services, as well as comparable access to health screenings.

Those topics were part of the discussion at the White House meeting, and Dr. Turek said stakeholders who attended continued to discuss the need for an Office of Men’s Health even after the meeting concluded. Whether this discussion and the White House conference leads to action on this and other initiatives focused on men’s health remains to be seen.

“If you want to take great care of men, you need to engage them, and to engage them, you need to listen,” Dr. Turek explained. “My office visits begin with listening, not talking.”

Bob Gatty

UT Washington Correspondent

Bob Gatty, a former congressional aide, covers news from Washington for Urology Times.
Malpractice Consult

Brianne Goodwin, RN

Ms. Goodwin is an attorney with Carter Conboy Attorneys and Counselors at Law in Albany, NY.

The malpractice suit: Why expert witness selection is crucial

Detailed familiarity with deposition testimony, medical facts also key to successful defense

In my previous column (“You’ve been sued for malpractice: What happens next,” January 2016, page 32), I provided a brief overview of the anatomy of the malpractice lawsuit. In this column, I will discuss expert witnesses and preparing for trial in a medical malpractice case.

Expert testimony is almost always necessary in a malpractice case, and the importance of selecting an appropriate expert cannot be understated. According to an article in a leading orthopedics journal: “In professional negligence cases, such as medical malpractice lawsuits filed against physicians, the specific duty owed by the physician to the patient is defined by the profession itself. A member of the profession is needed to tell the judge and jury what the defending physician should have done or not done under the particular circumstances, and whether such conduct constituted negligence by violating the standards of care of the profession” (Clin Orthop Relat Res 2009; 467:339–47).

Much like the stream on a uroflow, expert witnesses can be either weak or strong. If a proper expert is not known to the attorney, he or she should spend some time vetting individual physicians. This might include:

• researching their education, including any fellowships performed
• establishing board certification in the relevant field
• reviewing publications and book chapters
• comparing his or her level of expertise to that of the client
• determining if any state has disciplined him or her
• investigating how many times he or she has served as an expert witness.

It should be stressed that the prominence alone of a particular physician does not necessarily make him or her the best expert witness for your case. For example, the literature demonstrates that the debate over partial versus radical nephrectomy for certain renal tumors continues to thrive. If a physician is sued for alleged malpractice stemming from a radical nephrectomy, the defense attorney would be keen to avoid any urology expert who unequivocally feels that a partial nephrectomy is superior to a radical.

Any skilled plaintiff’s attorney will be able to elicit this opinion as a weakness on cross-examination, likely compromising the expert’s credibility before the judge and jury. Furthermore, this individual would lack the requisite impartiality to serve as an expert witness, as set forth in the AUA policy statement regarding expert witness testimony.

Knowledge of potential jury pool vital

Another important consideration with regard to expert witnesses is that the attorney know the characteristics of the potential jury pool. Is the jury likely to be more or less educated? Just as the urologist in the office will tailor education differently to a patient with a high school degree versus a college degree, the expert witness must do the same to effectively reach and meaningfully communicate with the jury. This may require careful and detailed coaching by an attorney at times.

Preparing for trial can be arduous but is important for success. As the defendant physician, you should know your deposition testimony, the medical facts of the case, and the medical literature on both sides of the pertinent issues as well as possible. It is likely that the plaintiff’s attorney will try and undermine your credibility using either your deposition, the medical chart, or some claim within the literature, so a lack of knowledge in one or more of these areas could make for a challenging cross-examination.

A simple example of this:

Q: Doctor, is it true that part of the standard of care in medicine is good documentation?

A: Yes.

Q: Doctor, is it also true that you failed to document the informed consent process as it relates to the plaintiff’s March 2, 2014 robotic prostatectomy?

A: Assuming documentation of the informed consent process is at issue in the case, how you answer this question is important, as it will either support what was stated during the deposition or it will contradict it.

A contradiction will likely lead to the plaintiff’s attorney showing your deposition testimony as an exhibit (in blow-up format) to the jury and attempts to impeach your credibility on the witness stand. Even if documentation is a weakness in the case, it is best to support your deposition testimony so that the jury views you as credible and truthful. Weaknesses can often be clarified and supplemented at trial with information that was not elicited at the deposition (Brenner IR. “How to Survive a Medical Malpractice Lawsuit: The Physician’s Roadmap for Success.” Wiley-Blackwell, 2010).

Mock cross-examination can be helpful

Mock cross-examination by your own attorney may be a helpful tactic to simulate what will happen in the courtroom. This is a good strategy to gauge your ability to answer difficult questions and maintain composure at challenging times. It is also helpful for building your own confidence and oral advocacy skills.

Do you remember DRIP—a mnemonic representing general causes of incontinence: Delirium, Retention, Inflammation/Infection, and Polyuria? It can quickly be converted into a legal mnemonic summarizing the following important factors in trial preparation:

Designate proper expert

Review (and master) transcripts, facts, and literature

Increase confidence through mock questioning,

Professional presentation at trial.

There is no sugarcoating the fact the preparation for trial is a formidable and stressful period for any physician. Hopefully, the tips and examples provided here demonstrate the legal strategy behind selecting an expert for the case and show why it is necessary to resort back to medical school tactics for memorizing case facts and deposition testimony.
Pregnancy

The risk of fetal harm is unknown. Use in women who are or may become pregnant is not recommended. Pregnancy 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.

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/tiredness, back pain, decreased appetite, constipation, decreased libido, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension, and dizziness/flutter.

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 with 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 in 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% higher frequency in the XTANDI arm compared to the placebo arm.

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% higher frequency in the XTANDI arm compared to the placebo arm.

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<th>Condition</th>
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<th>Placebo N = 800</th>
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*Table 1. Adverse Reactions in Study 1 (cont.)*
Table 2. Adverse Reactions in Study 2 (cont.)

<table>
<thead>
<tr>
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<tr>
<td>Abnormal creatinine</td>
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<td>Neutropenia</td>
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<tr>
<td>Seizures</td>
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<td>Administration of XTANDI for more than 1 week</td>
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<tr>
<td>Hypertension</td>
<td>12%</td>
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</table>

**Laboratory Abnormalities**

In the two randomized clinical trials, Grade 1-4 neutropenia occurred in 15% of patients treated with XTANDI (1% Grade 3-4) and in 6% of patients treated with placebo (0.5% Grade 3-4). The incidence of Grade 1-4 thrombocytopenia was 6% of patients treated with XTANDI (0.3% Grade 3-4) and 5% of patients treated with placebo (0.5% Grade 3-4). Grade 4-1 elevations in ALT occurred in 10% of patients treated with XTANDI (0.2% Grade 3-4) and 15% of patients treated with placebo (0.2% Grade 3-4). Grade 4-1 elevations in bilirubin occurred in 3% of patients treated with XTANDI (0.1% Grade 3-4) and 2% of patients treated with placebo (no Grade 3-4).

**Infections**

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

**Fails and Related Injuries**

In the two randomized clinical trials, no patients were included with hypoventilation, asthenia, fatigue, and sudden death.

**Metastatic Disease**

No patients experienced metastatic disease crisis.

**Hypertension**

In the two randomized trials, hypertension was reported in 11% of patients receiving XTANDI and 4% of patients receiving placebo. No patients experienced hypertensive crisis.

**Post-Marketing Experience**

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

**Neurological Disorders: posterior reversible encephalopathy syndrome (PRES)**

**Drug Interactions**

**Drugs that Inhibit CYP2C8**

Co-administration of a strong CYP2C8 inhibitor (gemfibrozil) increased the Cmax of enzalutamide by 2.2-fold. Co-administration of XTANDI with strong CYP2C8 inhibitors should be avoided if possible. If co-administration of XTANDI with a strong CYP2C8 inhibitor cannot be avoided, reduce the dose of XTANDI.

**Drugs that Induce CYP3A4**

Co-administration of rifampin (a strong CYP3A4 inducer and moderate CYP2C9 and CYP2C19 inhibitor) decreased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 37%. Co-administration of strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin) with XTANDI should be avoided if possible. If co-administration of a strong CYP3A4 inhibitor with XTANDI cannot be avoided, increase the dose of XTANDI.

**Effect of XTANDI on Drug Metabolizing Enzymes**

Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inhibitor. At steady state, XTANDI reduced the plasma exposure to midazolam (CYP344 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate). Concomitant use of XTANDI with narrow therapeutic index drugs that are metabolized by CYP344 (e.g., alfacalcidol, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephénytoin) should be avoided, as enzalutamide may decrease their exposure. 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 an androgen receptor inhibitor could affect development of the fetus. Enzalutamide caused embryo-fetal toxicity in mice at exposures that were lower than those in pregnant women. 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, cleft palate and absent palate bone at 30 mg/kg/day. Doses of 30 mg/kg/day caused maternal toxicity. The doses tested in mice (1, 10 and 30 mg/kg/day) resulted in systemic exposures (AUC) approximately 0.04, 0.4 and 1.1 times, respectively, the exposures in patients. Enzalutamide did not cause developmental toxicity in rabbits when administered throughout the period of organogenesis (gestational days 6–18) at doses 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] < 89 mL/min) compared to patients and volunteers with baseline normal renal function (CrCl ≥ 90 mL/min). No initial dosage adjustment is necessary for patients with mild to moderate renal impairment. Severe renal impairment (CrCl < 30 mL/min) and end-stage renal disease have not been assessed.

**Patients with Hepatic Impairment**

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

**OVERDOSAGE**

In the event of an overdose, stop treatment with XTANDI and initiate general supportive measures taking into consideration the half-life of 5.8 days. In a dose escalation study, no seizures were reported at ≤ 240 mg daily, whereas 3 seizures were reported, 1 each at 360, 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, hypopermeatogenesis and atrophy of the prostate and epididymides were observed at ≥ 4 mg/kg/day (0.3 times the human exposure based on AUC).

Manufactured by: Catalent Pharma Solutions, LLC, St. Petersburg, FL 33716

Manufactured for and Distributed by: Astellas Pharma US, Inc., Northbrook, IL 60062

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

Medivation, Inc., San Francisco, CA 94105

Revised: October 2015

15018-XTA

Rx Only

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XTANDI® is a registered trademark of Astellas Pharma Inc.
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 in patients receiving XTANDI. Seizure occurred in 0.3% of placebo patients. There is no clinical trial experience in patients who developed a seizure. In Study 1, 1 patient in each treatment group (0.1%) had an infection resulting in death. 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.

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 a seizure during treatment.

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 for 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.

- 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 XtrandHCP.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.