TELE-UROLOGY moves from concept to practice

New PCa biomarker shows high specificity

Wayne Kuznar | UT CORRESPONDENT

New Orleans—The cell surface amino acid glypican-1 (GPC-1) represents a potential new biomarker for prostate cancer, said Jonathan Henderson, MD, at the AUA annual meeting.

A pilot study conducted in 345 men older than 50 years found high specificity of GPC-1 for prostate cancer. Its likely clinical use will be as an adjunctive test to patients with an elevated level of PSA, said Dr. Henderson, a urologist at Regional Urology in Shreveport, LA.

“The take-home message we found with this test is that the clinical utility is a high specificity,” he said. “We think we can use

Please see BIOMARKER, page 38

National Report—Peter N. Bretan, Jr., MD, professor of urology at Touro Medical School in Vallejo, CA, has privileges at nine, mostly rural hospitals. He’s the only urologist at six of those.

“There isn’t enough business at the hospitals to keep urologists solvent,” Dr. Bretan said. “But, if I can cover them instantaneously with telemedicine, I can capture the care and keep patients local—close to their families and primary care physicians.”

Dr. Bretan is part of a growing trend to provide health care via telemedicine.

Please see TELEMEDICINE, page 32

Hypospadias

A practical guide to preoperative counseling, surgical technique, and current controversies

CODING AND REIMBURSEMENT

19 ICD-10: Different codes but identical guidelines

MALPRACTICE

23 Nephrectomy gone wrong leaves patient paraplegic

PRACTICE MANAGEMENT

28 mCRPC advances come with choices, challenges

Varicocelectomy on YouTube

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Dr. Google creates anxiety, opportunity

The most popular physician in the United States is Dr. Google. Most health information seekers navigate the Internet for what they think will be the best information available about their health condition or that of a loved one. Unfortunately, the Internet is unfiltered, unregulated, and often saturated with promotional, unsubstantiated, and at times frightening information.

If you do a Google search for prostate cancer, for example, you’ll turn up 29.8 million results. For testosterone therapy, you’ll get 16,500,000 results. In the past, patients often received their first information from their health care provider. Today, many come to the doctor’s office with stacks of files on condition accrued from web searches.

Testosterone therapy is a particularly challenging area because men feel vulnerable about aging and are ripe for being influenced by advertising, misinformation, and even outright lies in their quest to recapture their youth. In their study, the authors noted that much of the information is directed non–physicians, even though disclosure of financial interests in the products being touted. In only about 27% were side effects discussed.

Some call this shameful; others call it capitalism. There is much financial gain to be made in an arena where the science is at best evolving with lots of questions and few definitive answers. So where do we go from here?

Dr. Google takes enormous effort and creates alarming degrees of anxiety and frustration. People are overwhelmed and don’t know whom to trust and what applies to them. However, this is an ideal opportunity for urologists and other health care providers to offer a better benefit to their patients. Providing accurate and timely information and interdigitating modern technology to deliver curated meaningful informations will, in time, overcome the overwhelming data dump one gets on the Internet.

We will never be able to rid ourselves of the charlatans and those who prey on the vulnerable, sick, and elderly. However, we can and must optimize our interactions with patients and provide a more seamless approach to their health care delivery.

Dr. Steven Kaplan, MD

Steven Kaplan, MD

Dr. Kaplan is the Director of Urology at Weill Cornell Medical College and the director of the Icahn Center's Men's Health Center, New York Presbyterian Hospital, New York City.

This is an ideal opportunity for urologists and other health care providers to offer a greater benefit to their patients.

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Dr. Kaplan’s quest to recapture his youth. In his study, the authors noted that much of the information is directed to non–physicians, even though disclosure of financial interests in the products being touted. In only about 27% were side effects discussed.

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BLOG

AUA 2015 notable for PSA paper, difficult live surgery

For blogger Henry Rosevear, MD, a handful of presentations at the recent AUA annual meeting stood out from the crowd and changed the way he practices medicine. Among them: a paper that validated his concerns about PSA testing by primary care doctors and a live surgery case that didn’t go quite as planned.

READ DR. ROSEVEAR’S AUA TAKE-AWAYS AT: urologytimes.com/AUAtakeaways

REACTION

End of fee for service equals government takeover

Our April 1 cover article, “Say farewell to fee for service,” drew strong reaction from readers. All are skeptical that the shift to value-based care will improve health care. Said one: “The end of fee for service is exactly what our government overlords want: a complete government takeover of the medical profession.”

urologytimes.com/feeforservicereaction

VIDEO

What King v. Burwell could mean for your practice

The Supreme Court will soon rule on King v. Burwell, which challenges whether tax subsidies helping Americans purchase health insurance through healthcare.gov are valid. In this video, Anders M. Gilberg of the Medical Group Management Association examines what a decision invalidating those subsidies would mean for medical practices.

don不克older.com/kingburwell

UT FOLLOWER OF THE MONTH

@MacalusoJoseph

Joseph N. Macaluso, Jr, MD, a New Orleans urologist, is the Urology Times Twitter follower of the month! To be featured in this section, engage with us.

Our followers tweet about renal masses and more

Scott Eggener
@uroegg
Please people, come to your senses: not everyone diagnosed with renal mass on CT needs an MRI!!!

Henry Woo
@DrHWoo
With bullying/harassment in surgery in spotlight, some specialties were notorious. In my training days cardiac surgeons had a god complex.

Christopher Bayne
@chrbayne
Don’t understand why patients dislike Ensure and Boost. I love ‘em

daviesbj
@daviesbj
I’m not religious at all but I do love it when patients families say “God bless you”. Go figure.

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Promoting TRT online: Balanced information lacking

Most websites run by nonspecialists, fail to mention risks of treatment

Lisette Hilton
UT CORRESPONDENT

Chicago—Patients taking to the Internet for information about testosterone replacement therapy (TRT) are likely getting an incomplete picture of the potential risks and adverse effects linked with the treatment, say researchers from Northwestern University Feinberg School of Medicine, Chicago, and the University of Pennsylvania, Philadelphia.

Hypogonadism

As testosterone replacement has become a popularized and controversial topic in recent years, the authors sought to explore what information patients will encounter when they search the Internet for providers of TRT.

About one-fourth of sites discuss risks

The research, which was recently published in *Urology* (2015; 85:814-8), evaluated 75 websites and found that the majority were run by nonspecialists, either nonphysicians (36%) or nonurology or nonendocrine physicians (47%). Further, although nearly all (95%) discussed the potential health benefits of TRT, mentioning improvements in sex drive, cognitive function, muscle strength, and/or energy, only about one-fourth provided specific information about TRT’s potential risks. The websites directed by urologists or endocrinologists were twice as likely to provide information about potential risks compared to those of the nonspecialists. Nevertheless, possible adverse effects were still only mentioned on 41% of the specialists’ websites.

Speaking to *Urology Times*, lead author Daniel T. Oberlin, MD, said that irrespective of website content, he and his co-authors suspect that most providers have a comprehensive discussion about the potential risks and benefits of TRT with patients during clinical encounters. However, the study’s findings raise concern about the information patients are accessing as they consider therapeutic options.

“We urge all providers of TRT to provide balanced information to patients, and encourage urologists, in particular, to champion their web presence and help optimize the quality and quantity of information available about TRT,” said Dr. Oberlin, urology resident at Northwestern, who worked on the study with Robert E. Brannigan, MD, Puneet Masson, MD, and co-authors.

The websites evaluated in the study were identified by a Google search performed in November 2013 using the term “testosterone replacement” and the names of the five most populous U.S. cities (New York, Los Angeles, Chicago, Houston, and Philadelphia). The top 15 unique websites for each city returned in the search were included.

Some sites refute TRT risks

A more detailed analysis of website content on potential risks showed that not only did about three-fourths of sites not discuss potential risks of TRT, but nine (12%) actually refuted that TRT could be associated with adverse events. Infertility was the most common potential side effect described overall, being mentioned on 41% of specialists’ websites but only about 13% of nonspecialists’ sites overall. Gynecomastia was the second most commonly mentioned potential risk and was identified by 31% of specialists’ websites and 16% of nonspecialists’ websites. Potential cardiovascular risks were mentioned on 12% of specialists’ websites and on none of the websites under nonspecialist direction.

“As has been made evident by recent FDA Drug Safety Communications, the jury is still out on the possible cardiovascular risks of TRT, and questions about any associations with heart attack or stroke will remain largely unanswered until we have data from well-designed clinical trials,” Dr. Oberlin said. “In the meantime, urologists should help distill the available information regarding these and other potential risks to patients, providing a balanced framework in which they can consider therapeutic options.”

Dr. Oberlin and colleagues consider their assessment timely and important, recognizing how patients are increasingly turning to the Internet as a source for health and medical information and considering that TRT providers seemed to be working to increase their web presence.

InBrief

UT names three to Council

*Urology Times* has appointed three expert urologists to its Editorial Council: Jeffrey E. Kaufman, MD, a private practitioner in Santa Ana, CA; Arthur L. Burnett, II, MD, MBA, of Johns Hopkins Medicine, Baltimore; and Barry A. Kogan, MD, of Albany Medical College, Albany, NY.

Drs. Kaufman, Burnett, and Kogan will represent the areas of health policy/socioeconomics, sexual dysfunction, and pediatric urology, respectively. *Urology Times* also extends its gratitude and appreciation to William F. Gee, MD, John J. Mulcahy, MD, PhD, Howard M. Snyder, III, MD, and Anthony J. Schaeffer, MD, who recently stepped down after many years of dedicated service to the Editorial Council.
No credible... evidence’ linking T to PCa

Long-term TRT study refutes prostate safety concerns

Cheryl Guttman Krader
UT CONTRIBUTING EDITOR

New Orleans—Data from a single center’s growing cohort of hypogonadal men provide additional evidence supporting the prostate safety of testosterone replacement therapy (TRT).

At the AUA annual meeting, Ahmad Haider, MD, PhD, presented outcomes from analyses of data collected for 347 men who are part of a longitudinal observational registry study being conducted in his private practice in Bremerhaven, Germany.

All patients had a testosterone level ≤350 ng/dL at entry. They had a mean age of 57 years and were started on testosterone undecanoate (TU [AVEED]), 1,000 mg injections given every 12 weeks after 2 loading doses at 0 and 6 weeks.

Maximum follow-up has now reached 87 months, 67 men had reached the 84-month visit, and the total follow-up for the cohort is 1,806 person-years.

During the available follow-up, prostate cancer was diagnosed in six men (1.7%). Time to diagnosis was 10 to 19 months after TRT initiation, the diagnosis in all men was made following an increase in PSA, and maximum Gleason score was 3+3.

All patients underwent radical prostatectomy. Pathologic T stage was pT2a in four men, pT2b in one, and pT1b in one. TRT was temporarily interrupted, but resumed by five of the six men, Dr. Haider reported.

“The incidence of prostate cancer in our population was calculated as 27.7 per 10,000 patient years, which is far below the incidence reported in large screening studies,” he said, citing the Prostate, Lung, Colorectal, and Ovarian Cancer screening trial and the European Randomized Study of Screening for Prostate Cancer.

Time for a ‘paradigm shift’

Abdulmaged M. Traish, MBA, PhD, professor of urology and biochemistry at Boston University School of Medicine, was a co-author of the paper. Speaking to Urology Times, he said, “Androgen deprivation therapy has been used in the management of prostate cancer for more than 7 decades based on the concept that testosterone causes prostate cancer development and progression. During that time, there is no evidence that quality of life or survival has improved with ADT,” Dr. Traish said.

“Now it is time to have a paradigm shift in our view of the relationship between testosterone and prostate cancer. Clearly, there is no credible scientific or clinical evidence that links testosterone to development or progression of prostate cancer. The time has come to train the new generation of clinicians and scientists in the light of the new paradigm and leave the old myth behind.”

Aside from the patient with prostate cancer who did not go back on TRT, all of the hypogonadal men who started on TRT are continuing with their TU injections. At the

Please see TRT, page 12

Urology Times

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Infection

Searching the nationwide MarketScan database for the years 2003 to 2011, the study identified 28,545 women with incident uncomplicated recurrent UTIs, defined as three office or ER visits with an ICD-9 code for UTI associated with a prescription for antibiotics during a 12-month period in the absence of a UTI in the year preceding the first UTI and any complicating factors.

The workup included at least one urine culture in 61% of women, imaging in 6.9%, and cystoscopy in 2.8%. Overall, 33.2% of women identified as having culture-directed care defined by having a urine culture associated with >50% of their UTIs. Relative to a propensity score-matched control group of women who did not receive culture-directed care, women who did have such care had significantly fewer ER visits with an ICD-9 code for UTI-related hospitalizations and a significantly lower rate of treatment with intravenous antibiotics.

“Guidelines on management of uncomplicated recurrent UTI, which are available from the Canadian Urological Association and European Association of Urology, recommend obtaining a urine culture with each UTI and discourage the routine use of cystoscopy and urinary tract imaging,” said first author Anne Suskind, MD, MS, assistant professor of urology at the University of California, San Francisco.

“We believe these findings probably reflect slightly higher intensity of care and a higher acuity of the problem among women who received urine culture-directed care,” Dr. Suskind said.

The study was supported by the National Institute of Diabetes and Digestive and Kidney Diseases as part of the Urologic Disease of America Project.

High incidence of infection in study population

Culture-directed care underused in recurrent UTIs

Cheryl Guttmann Krader
UT CONTRIBUTING EDITOR

New Orleans—It is well recognized that uncomplicated recurrent urinary tract infections (UTIs) are a common and costly problem in the community. Research presented at the AUA annual meeting in New Orleans brings us a step toward better understanding the magnitude of the problem, practice patterns for patient evaluation, and their effect on downstream resource utilization.

TRT continued from page 7

time the analyses were performed, 209 men had been on treatment for 2 years, 122 were seen after 4 years, and 82 had reached the 5-year follow-up.

Other results showed mean PSA for the entire cohort increased slightly over time (+0.09 ng/mL). The change was not statistically significant. Mean prostate volume increased, but by only 2.46 mL, which is not clinically important, Dr. Haider said.

Analyses of International Prostate Symptom Score and postvoid residual bladder volume showed no evidence that TRT negatively affected voiding function. Mean International Prostate Symptom Score was around 6.5 at baseline and decreased progressively (improved) and significantly over the entire observation time. Postvoid residual bladder volume decreased significantly in parallel to IPSS, with a mean decrease of 34.17 mL.

C-reactive protein is also being measured during follow-up and showed a steady and statistically significant decrease over time. At 84 months, the mean change from baseline was −5.83 mg/dL.

Dr. Haider commented that some of the benefits occurring among the men being treated with TRT may be the result of anti-inflammatory effects of TRT and weight loss, which was also observed in the cohort.

UTSTAT

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Male pattern baldness linked to prostate Ca mortality
Findings suggest balding, PCa share pathophysiologic mechanisms

Alice Goodman
UT CORRESPONDENT

Philadelphia—A large prospective study suggests men with male pattern baldness (MPB), particularly moderate MPB, are more likely to die from prostate cancer, compared to men with no MPB.

Prostate Cancer

These findings support the hypothesis that MPB and prostate cancer share some pathophysiologic mechanisms, explained lead author Cindy Ke Zhou, PhD, post-doctoral fellow at the National Cancer Institute, Bethesda, MD, who worked on the study with Michael B. Cook, PhD, and co-authors.

There are few established risk factors for the development of prostate cancer. These include advancing age, African-American ancestry, and a family history of the disease.

“The associations found in our study are important. Male pattern baldness is known to be associated with ‘male’ sex hormones (andro gens) such as testosterone. We also know that testosterone is integral to prostate gland development and prostate cancer progression. We hope our findings will help guide mechanistic studies to uncover the relationship between androgens and this common malignancy among men,” Dr. Zhou said.

The same group of investigators previously showed an association between MPB at age 45 years and aggressive prostate cancer, published in the Journal of Clinical Oncology earlier this year (2015; 33:419-25). In that study, MPB was self-reported. The current study, which Dr. Zhou presented at the American Association of Cancer Research annual meeting in Philadelphia, is the first to look at prostate cancer-specific mortality, where MPB was assessed by dermatologists.

This study included 4,316 men from the NHANES-I Epidemiologic Follow-up Study, who were 25–74 years of age and had no prior cancer diagnosis at study enrollment. Participants joined the study between 1971 and 1974. Trained dermatologists assessed the degree of MPB at study enrollment. During a median follow-up of 21 years, 3,284 deaths occurred in this cohort, 107 of which were due to prostate cancer.

Balding increases death risk by 56%
In this analysis, men with any degree of MPB had a 56% increased risk of dying from prostate cancer compared to men with no balding. Men who had moderate MPB had an 83% increased risk of dying from prostate cancer, compared to men with no balding. The small number of patients with severe balding who died of prostate cancer limited the statistical power to detect a significant association for this category of hair loss. Conversely, MPB was not statistically significantly associated with all-cause mortality.

“Results from previous studies on the association between circulating sex steroid hormones and prostate cancer risks are inconsistent. These studies have looked at circulating sex steroid hormone concentrations in the blood at a single time-point among men at mid-life or older, and these studies may not have adequately captured the etiologically relevant time-window(s) of androgen exposure. Therefore, we used MPB as a proxy of long-term androgen exposure,” Dr. Zhou explained.

“These findings need to be replicated in future studies,” she added. “It is still premature to recommend any practice changes related to prostate cancer screening, given the moderate association observed in our study and relatively high prevalence of male pattern baldness in the Western population.”

Targeted PET imaging shows promise in prostate Ca
Novel compound identifies foci of disease not found on biopsy, data show

Alice Goodman
UT CORRESPONDENT

Philadelphia—A novel compound used with positron emission tomography imaging can identify foci of prostate cancer not found on biopsy of the prostate pre surgery or on the post-surgery specimen, according to a pilot study presented at the American Association of Cancer Research annual meeting in Philadelphia.

The technique utilizes TP3805, a Vasoactive Intestinal Peptide and Pituitary Adeny late Cyclase Activating Peptide Receptor 1 (VPAC1)—specific biomolecule labeled with Cu-64 when imaging patients with prostate cancer.

“VPAC1, a cell surface receptor, is over-expressed in prostate cancer and is a highly suitable target for imaging and treatment. VPAC1 is nonspecific and also upregulated in a variety of tumors,” said presenting author Edouard Trabulsi, MD, associate professor of urology at Kimmel Cancer Center at Thomas Jefferson University, Philadelphia.

The study builds on the work of Mathew Thakur, PhD, also of the Kimmel Cancer Center. Supported by the National Institutes of Health, Dr. Thakur and colleagues studied PET imaging with vasoactive intestinal peptide and VPAC1 in breast and lung cancer and found that it was “exquisitely sensitive” in identifying undiagnosed lesions, Dr. Trabulsi explained.

The first-in-human pilot study presented at AACR 2015 is the first to evaluate this technique in prostate cancer. The study included 25 men diagnosed with prostate cancer slated for radical prostatectomy imaged preoperatively with PET imaging targeting VPAC1. All men underwent conventional biopsy and surgery. The preoperative scans were compared with pathology of the surgical and biopsy specimens. Cu-TP305 imaging identified 66% more lesions than prostate biopsy histology and 30%
Quality-measure compliance not tied to PCa outcomes

Cheryl Guttman Krader
UT CONTRIBUTING EDITOR

New Orleans—Physician compliance with different quality indicators for localized prostate cancer care varies. However, while improving compliance may impact physician reimbursement in the recently established Merit-based Incentive Payment System, its relevance for ensuring delivery of quality care is unclear because increased compliance does not seem to influence patient-centered outcomes during the first 12 months after treatment.

That is the conclusion of study co-authors William Sohn, MD, and Daniel Barocas, MD, urologic oncologists from Vanderbilt University Medical Center, Center for Surgical Quality and Outcomes Research, Nashville, TN.

The research was presented at the AUA annual meeting in New Orleans.

“Quality indicators from national quality consortia were developed to be incorporated in the value calculation in medicine, which is the quotient of quality over cost. However, there are no studies validating that clinical outcomes are improved by complying with these measures for localized prostate cancer,” said Dr. Sohn, clinical instructor in urologic surgery at Vanderbilt.

Compliance with 6 indicators assessed

The research analyzed data from 2,781 participants in the population-based, prospective Comparative Effectiveness Analysis of Surgery and Radiation (CEASAR) study. Physician compliance with the following six quality indicators, which are endorsed by various national quality consortia, was assessed:

- avoidance of bone scan in men with low-risk tumors
- androgen deprivation therapy for high-risk patients undergoing radiation therapy
- documentation of clinical T stage and biopsy Gleason score at new diagnosis
- documentation of digital rectal examination, clinical T stage, and biopsy Gleason score prior to primary therapy
- documentation of discussion of treatment options
- documentation of pathologic T and N stage, Gleason score, and margin status on pathology report

The results showed the level of provider compliance with the different quality measures was variable, ranging from as low as 64% for documentation prior to primary therapy to 86% and 88% for documentation of discussion of treatment options and of pathologic data, respectively.

In the multivariable analyses, three of the six measures were weakly associated with 12-month sexual function and bowel function scores (β -4.6 and 1.69, 2.93, respectively; p≤0.05).

However, the differences in scores are unlikely to be clinically meaningful,” Dr. Sohn said.

There were no other significant relationships between the quality measures and patient-reported HRQoL outcomes, nor were satisfaction scores and treatment-related complications associated with quality measure compliance.

Limitations and future directions

Dr. Sohn acknowledged that the study does not tell the whole story, since it assessed the impact of compliance with the indicators on patient-reported HRQoL outcomes. These nationally endorsed process measures may be associated with other desirable quality goals; namely, effective clinical care, cost-effectiveness, and efficiency, rather than improved patient-reported outcomes, he said.

In addition, Dr. Sohn noted that compliance with the indicators might be relevant to outcomes in subgroups of vulnerable patients. The investigators did not identify any such effects based on age, race, or income level.

“Perhaps that is because of limited statistical power in these smaller subgroups. However, additional analyses could reveal certain high-risk sub-populations that may have improvements in HRQoL, satisfaction scores, and complications with quality measure compliance,” said Dr. Sohn.

“Our next steps are to try to figure out what influences quality measure compliance and if there are certain patient groups that benefit from improved compliance,” he told Urology Times.

“In addition, we will be looking at relationships between compliance and other outcomes, and ultimately see if we can develop other quality measures that are related to health-related quality of life.”

Targeted PET

continued from page 14

more lesions than whole mount radical prostatectomy histology.

Malignant lesions were those with standardized uptake values >100. A total of 212 lesions were deemed malignant compared with 127 identified by histology.

PCa foci identified in 98% of cases

Prostate cancer foci were identified by PET with VPAC1 in 98% of cases. Two lesions were missed due to technical artifact. Additionally, nine small cancerous lesions were identified on imaging that were not identified on examination of the biopsy slides. A total of 19 additional lesions seen on PET in areas without prostate cancer foci identified areas of high-grade pros tatic intraepithelial neoplasia. A positive lymph node and a benign lymph node were correctly identified by PET targeted to VPAC1.

The positive predictive value of the PET VPAC1-targeted imaging was 97% and the negative predictive value was 100%.

“The study validated VPAC1 as a potential target for prostate cancer and treatment,” Dr. Trabulsi said. “We found that we can accurately identify foci of prostate cancer within the gland prior to surgery. In fact, we were able to detect lymph node involvement in one patient not seen preoperatively.”

The next study planned is a trial of men with elevated PSA and previously negative biopsies to determine whether PET targeted to VPAC1 can identify areas of prostate cancer within the gland.

“Down the road, we envision studies in men with rising PSA after surgery or radiotherapy to delineate sites of disease, and also studies in metastatic disease to determine if we can assess burden of disease,” Dr. Trabulsi said. “Nirvana would be if we could conjugate VPAC1 to other radiotoxic isotopes for therapeutic purposes.”
Pediatric hypospadias repair in 2015

A practical guide to preoperative counseling, nuances of surgical technique, and current controversies

Mark A. Faasse, MD, MPH  •  Earl Y. Cheng, MD

Hypospadias affects between 1 in 125 and 1 in 300 males, resulting from premature arrest of urethral fold tubularization. Some evidence suggests that the number of hypospadias cases is rising, with potential reasons including in utero exposure to endocrine-disrupting chemicals, higher maternal age, and improved survival of infants with associated syndromes (J Urol 2012; 188:2362-6). However, this trend remains controversial and may simply reflect greater awareness and reporting of milder forms (European Urology Supplements 2012; 11:33-45).

This article provides a contemporary perspective on several aspects of hypospadias surgery, including preoperative counseling, use of androgen stimulation, and technical nuances for repair of routine midshaft-to-distal hypospadias, as well as more complex cases. A brief discussion of surgical outcomes and directions for future research is also included.

Preoperative counseling and timing of surgery

Patients with hypospadias usually present for evaluation as asymptomatic infants, and parents must decide whether to pursue surgery. Considerations include a desire to optimize future urinary function (i.e., being able to stand to void with a straight, directable stream) while preventing sexual dysfunction related to penile curvature, infertility related to inability to deposit semen in the vaginal fornix, cosmetic dissatisfaction, and psychosocial/sexual embarrassment.

The natural history of untreated hypospadias is poorly defined. However, the severity of impact on urinary and sexual function is likely to correlate with the location of the urethral meatus and the degree of ventral curvature. Limited survey data suggest that adults with coronal or glanular hypospadias are generally satisfied with penile appearance and have little or no clinically significant differences in urinary or sexual function compared to normal controls (Urology 2008; 71:682-5; J Pediatr Urol 2014; 10:672-9). In these cases, foregoing surgery or opting for meatoplasty, correction of ventral curvature, and/or circumcision versus foreskin reconstruction alone may be suitable, with lower risk of complications than complete hypospadias repair.

We generally perform primary hypospadias repair between 6 and 12 months of age. We defer repair at younger ages because of potentially higher risks related to anesthetic exposure and our desire to allow the penis to grow larger during the “mini-puberty” that occurs within the first 6 months of life.

Preoperative androgen stimulation

Prescription of testosterone (intramuscular or topical) or dihydrotestosterone (topical) within 1-3 months prior to surgery remains common to increase penile size and improve tissue characteristics; dosing regimens vary widely (J Pediatr Urol 2014; 10:672-9). This practice has become controversial in recent years, as some studies suggest that androgen stimulation may actually impair wound healing and be associated with higher risk of postoperative complications. However, all human clinical data to this effect have come from retrospective studies and are therefore vulnerable to selection bias and confounding factors, such as the severity of hypospadias and degree of ventral curvature. To date, the only randomized, controlled trial of preoperative androgen stimulation found topical dihydrotestosterone to have a significantly favorable impact on postoperative outcomes (J Urol 2008; 179:684-8). Unfortunately, dihydrotestosterone is not readily available in the United States.

Additional randomized, controlled trials in this area are clearly necessary. We now use preoperative androgen stimulation selectivity in cases where the glans is small and/or severe ventral curvature is present, when deficiency of skin for ventral coverage is of greater concern and need for vascularized skin flaps is more likely.

Repair of midshaft-to-distal hypospadias: TIP urethroplasty

Hundreds of papers have been published on surgical techniques and modifications for hypospadias repair. Today, most mid-to-distal hypospadias defects are addressed by tubularized incised plate (TIP) urethroplasty. Meatal advancement and glansplasty (MAGPI)
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.
In men with mCRPC who progressed on ADT, consider ZYTIGA® (abiraterone acetate) first.

Final analysis of the pivotal phase 3 trial.*

Every day tells a story.

IMPORTANT SAFETY INFORMATION

Increased ZYTIGA® Exposures With Food—ZYTIGA® must be taken on an empty stomach. No food should be eaten 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. Abiraterone Cmax and AUC0-∞ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state.

Adverse Reactions—The most common adverse reactions (≥10%) are fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection, and contusion.

The most common laboratory abnormalities (>20%) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT, and hypokalemia.

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

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

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

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

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.
After a median 4 years (49 months) of follow-up...

**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

**In your patients with mCRPC...**

**CONSIDER ZYTIGA® FIRST.**

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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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ZYTIGA® (abiraterone acetate) Tablets

Brief Summary of Prescribing Information.

INDICATIONS AND USAGE
ZYTIGA is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer.

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 pregnant or who 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 Full Prescribing Information (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].

Co-administration of a corticosteroid suppresses adrenocorticotropic 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 III or IV heart failure (in Study 1) or NYHA Class II to IV heart failure (in Study 2) was not established 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: Adrenal insufficiency occurred in the two randomized clinical studies in 0.5% of patients taking ZYTIGA and in 0.2% of patients taking placebo. Adrenocortical insufficiency was reported in patients receiving ZYTIGA in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations [see Warnings and Precautions].

Hepatotoxicity: In the two randomized clinical trials, grade 3 or 4 ALT or AST increases (at least 5X ULN) were reported in 4% of patients who received ZYTIGA, typically during the first 3 months after starting treatment. Patients whose baseline ALT or AST were elevated were more likely to experience liver test elevation than those beginning with normal values. Treatment discontinuation due to liver enzyme increases occurred in 1% of patients taking ZYTIGA. No deaths clearly related to ZYTIGA were reported due to hepatotoxic 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 250 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 functional 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.

Increased ZYTIGA Exposures with Food: ZYTIGA must be taken on an empty stomach. No food should be consumed for at least two hours before the dose is taken. ZYTIGA should be administered with a meal compared to a fasted state. The safety of these increased exposures when multiple doses of abiraterone acetate are taken with food has not been assessed [see Dosage and Administration (2.1) and Clinical Pharmacology (12.3) in full Prescribing Information].

ZYTIGA® (abiraterone acetate) Tablets

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].
- Increased ZYTIGA Exposures with Food [see Warnings and Precautions].

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

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

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

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, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, 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>Adverse reaction</td>
<td>All Grades</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Muscle/skeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint swelling/discomfort</td>
<td>29.5</td>
<td>4.2</td>
</tr>
<tr>
<td>Muscle discomfort</td>
<td>26.2</td>
<td>3.0</td>
</tr>
<tr>
<td>General disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>26.7</td>
<td>1.9</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot flush</td>
<td>19.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8.5</td>
<td>1.3</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>6.1</td>
<td>0</td>
</tr>
<tr>
<td>Infections and 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>Cardiac disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>7.2</td>
<td>1.1</td>
</tr>
<tr>
<td>Chest pain or chest discomfort</td>
<td>3.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>2.3</td>
<td>1.9</td>
</tr>
</tbody>
</table>

1. Adverse events graded according to CTCAE version 3.0
2. Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness
3. Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Musculoskeletal discomfort, and Musculoskeletal stiffness
ZYTIGA® (abiraterone acetate) Tablets

Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema

Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness

Includes terms Angina pectoris, Chest pain, and Angina unstable.

Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomyopathy, and Ejection fraction decreased

Includes all fractures with the exception of pathological fracture

Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema

than or equal to 5% rate in the ZYTIGA arm. Median duration of treatment with ZYTIGA was 13.8 months.

Table 3 shows adverse reactions on the ZYTIGA arm in Study 2 that occurred in 0.2% of patients taking placebo. There were no treatment discontinuations and one death due to cardiac failure in the placebo group.

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

System/Organ Class
Abiraterone (N=791) Placebo (N=394)

Laboratory Abnormality

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>All Grades (%)</th>
<th>Grade 3-4 (%)</th>
<th>All Grades (%)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertriglyceridemia</td>
<td>62.5 (0.4)</td>
<td>53.0 (0)</td>
<td>30.6 (2.1)</td>
<td>36.3 (1.5)</td>
</tr>
<tr>
<td>High AST</td>
<td>28.3 (5.3)</td>
<td>19.8 (1.0)</td>
<td>23.8 (7.2)</td>
<td>15.7 (5.8)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>11.1 (1.4)</td>
<td>10.4 (0.8)</td>
<td>6.6 (0.1)</td>
<td>4.6 (0)</td>
</tr>
</tbody>
</table>

Study 2: Post Market Experience

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

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Abiraterone (N=542)</th>
<th>Placebo (N=540)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphopenia</td>
<td>38.2 %</td>
<td>8.7 %</td>
</tr>
<tr>
<td>Hyperglycemia</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>

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 treatment discontinuations and 2 deaths. Grade 3-4 cardiac failure occurred in 0.2% of patients taking placebo. There were no treatment discontinuations and one death due to cardiac failure in the placebo group.

In Study 1 and 2, the majority of arrhythmias were grade 1 or 2. There was one death associated with arrhythmia and one patient with sudden death in the ZYTIGA arms and no deaths in the placebo arms. There were 7 (0.5%) deaths due to cardiorespiratory arrest in the ZYTIGA arms and 3 (0.3%) deaths in the placebo arms. Myocardial ischemia or myocardial infarction led to death in 3 patients in the placebo arms and 2 deaths in the ZYTIGA arms.

Post Marketing Experience

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

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

DRUG INTERACTIONS

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

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

Effects of Abiraterone on Drug Metabolizing Enzymes: ZYTIGA is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8. In a CYP2D6 drug-drug interaction trial, the Cmax and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine).

If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug [see Clinical Pharmacology (12.3) in full Prescribing Information].

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone (CYP2C8 substrate) was increased by 46% when pioglitazone was given together with a single dose of 1,000 mg abiraterone acetate. Therefore, patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with ZYTIGA [see Clinical Pharmacology (12.3) in full Prescribing Information].
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 1, 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 ano-genital distance at ≥30 mg/kg/day, and decreased fetal body weight at 100 mg/kg/day. Doses ≥10 mg/kg/day caused maternal toxicity. The doses tested in rats resulted in systemic exposures (AUC) approximately 0.03, 0.1 and 0.3 times, respectively, the AUC in patients.

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 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.
remains applicable to glanular hypospadias, and some surgeons continue to use perimeatal-based flaps for urethroplasty (“flip-flap repair”). However, it is generally acknowledged that TIP repair achieves better cosmesis in terms of a vertically oriented, slit-like urethral meatus.

Detailed descriptions of TIP repair have previously been published with excellent illustrations (J Urol 1994; 151:464-5; BJU Int 2005; 95:683). Our objective is to supplement rather than replicate the content of these articles. From the outset, it is helpful to keep in mind the overarching surgical aims:

- correction of ventral curvature (orthoplasty)
- repositioning the urethral meatus as close as possible to the tip of the glans penis (urethroplasty)
- constructing a conical glans (glansplasty)
- skin coverage of the penile shaft.

Key principles include maintaining vascular supply to all tissue and achieving tension-free, non-overlapping suture lines. Use of loupe magnification or an operating microscope is standard.

The importance of properly planning the initial skin incisions cannot be overstated. After placing a glans retraction suture, we pass an 8F bougie à boule to gauge the quality of urethral tissue proximal to the existing meatus. In some cases, this tissue is nearly see-through, and the skin incision should be marked more proximally at the point where more robust tissue is present. (Photo courtesy of Elizabeth B. Yerkes, MD)

Regardless of whether foreskin reconstruction (J Urol 2001; 165:1255-7) or circumcision is intended, marking the remainder of the initial incision is made easier by placement of holding sutures through the distal-most aspect of the prepuce on either side of the ventral deficiency. An adequate amount of “mucosal collar” is preserved for circumcision by marking the dorsal skin incision with a wide-based chevron (figure 2A). Ventrally, the incision follows the mucosal-skin margin (figure 2B). This results in “wings” of extra mucosal tissue on each side (figure 2C). If the urethral meatus is proximal to the corona or a cutback is planned, the initial incision must be carried proximal to the meatus (or point of cutback) in a U-shape, ideally maintaining at least a 10-mm width for the urethral plate (figure 2D).

While incising and degloving the penis, great care must be taken to avoid inadvertent urethrotomy, as there may be little or no tissue between the skin and urethra because of divergent spongiosum. Dissection can be aided by placing a catheter in the urethra and, most important, putting the overlying skin on sufficient traction. We use stay sutures for this purpose. Initial dissection must remain as superficial as possible under the skin until the desired plane is established.

Degloving the penis usually provides adequate correction of ventral curvature associated with distal hypospadias. For mid-shaft or more proximal defects, an artificial erection may be performed with application of a tourniquet and instillation of injectable saline into the corpora cavernosa. Residual curvature can be addressed by dorsal plication at the point of maximal curvature. Plication sutures are placed in the midline to avoid injury of the neurovascular complex on the dorsolateral surface of the penile shaft.

Overly aggressive plication may result in kinking of the dorsal arterial blood supply to the glans penis. Therefore, glans perfusion should be reassessed later in the case after glans wing mobilization. On occasion, the plication suture needs to be removed or placed less aggressively to preserve glanular perfusion.

Once the penis is straight, attention is turned to preparation of the urethroplasty. For hemostasis, a tourniquet may be applied or the glans can be injected with lidocaine/epinephrine Please see HYPOSPADIAS, page 18
along either side of the urethral plate. We mark the intended incisions of the glans on either side of the urethral plate with a hashmark to define our intention for the distal-most extent of the subsequent urethroplasty (figure 3). Note that the glans incision proceeds slightly beyond this point.

TIP derives its name from midline incision of the urethral plate, which facilitates tension-free tubularization of the plate margins. This incision should not extend distal to the urethral plate. Some surgeons prefer to incise the plate prior to making the glans incisions, so that the laterality of the glans incisions can be adjusted if the midline incision provides less laxity than anticipated. However, our experience has been that sufficient relaxation of the urethral plate can be obtained regardless of the width of the urethral plate simply by incising it deeply. The glans wings must be adequately mobilized by dissecting down to the tips of the corporal bodies and then slightly lateral and distal.

Tubularization of the neourethra can be performed around a 6-8F stent, using continuous or interrupted 6-0 or 7-0 absorbable sutures, such as polyglactin or polidioxanone. Subepithelial suture placement inverts the epithelial edges. The urethroplasty is then covered by a dartos flap (J Urol 2001; 163:1536-9). Tension-free midline approximation of the previously mobilized glans wings is then performed.

Following glansplasty, the final step of repair is tailoring of the penile skin for coverage of the shaft. It may be necessary to create Byar’s flaps by incising excess dorsal skin in the midline and wrapping the resulting skin flaps around to the ventrum of the penis. We apply a gentle compression dressing for 2-4 days to ensure hemostasis and reduce edema.

### TIP urethroplasty: Postoperative care

We routinely leave the urethral stent in place for 5 to 10 days after TIP repairs. It remains unclear whether this practice decreases urethroplasty complications. However, it eliminates the possibility of acute urinary retention and potential need for postoperative catheterization through the newly constructed urethra.

Another controversial practice is use of prophylactic antibiotics for the duration of urethral stenting. We have initiated a multicenter, placebo-controlled trial to investigate the impact of prophylaxis on both infectious and wound-healing complications.

### Proximal and reoperative hypospadias repair

Proximal and complex reoperative hypospadias repairs continue to be a challenging aspect of pediatric urology. In select cases, TIP urethroplasty can also be used for single-stage correction of proximal hypospadias, with limitations imposed by the degree of ventral curvature and quality of the urethral plate. When curvature exceeds 30° after degloving the penis, dorsal plication is suboptimal and transection of the urethra is advised, committing the patient to a staged repair.

After transecting the urethra, residual curvature can be addressed in one of two ways. The first option is corporal body grafting. This is performed by making a single full-thickness incision of the tunica albuginea from 3 to 9 o’clock on the ventrum of the penis, opposite the point of maximal curvature. The tunica is mobilized from underlying corporal tissue for a few millimeters in each direction, and a diamond-shaped piece of small intestinal submucosa (SIS) or tunica vaginalis is inserted into the resulting defect. Alternatively, several nearly full-thickness incisions (“fairy cuts”) can be made in the tunica albuginea without grafting.

There are also several options for bridging the defect between the proximal edge of the urethral plate and the glans penis. We prefer using a rotational, dartos-based flap of preputial skin or Byar’s flaps; in most cases, the mucosal portion of prepuce proximal to the chevron incision portrayed in figure 2A will suffice. We also typically incise the midline of the urethral plate in the glans at the time of the first stage and incorporate the flap into this defect. Alternatively, a buccal graft may be used for the neourethra, as long as corporal body grafting was not performed. The remaining penile skin is then approximated to the lateral margins of the rotated flap or graft, and the neourethra is completed by tubularization during a second stage at least 6 months later.

When approaching reoperative hypospadias repairs, suitability of the native urethral plate for re-use must be carefully assessed. If any scarring is palpable more than 6 months after primary repair, we have a low threshold for excising the native plate and using buccal graft in a staged approach. Clinically significant residual penile curvature must be corrected prior to placement of the graft. Neourethral coverage with a well-vascularized tunica vaginalis flap should be considered when penile dartos has previously been harvested.

### Outcomes of hypospadias repair

Complication rates and cosmetic outcomes of mid-to-distal hypospadias repairs have improved considerably in recent decades. A recent population-based analysis suggests that only 5%-10% of these patients require reoperation (J Urol 2013; 190:251-6).

Unfortunately, reoperation rates for proximal repairs continue to be much higher, approaching or even exceeding 50% in some series. Long-term outcomes of modern surgical techniques are beginning to emerge, including patients’ self-assessment of urinary and sexual function and cosmesis as adults, but these data remain incomplete. Of particular concern to us are the durability and impact on erectile function of techniques currently being used for correction of ventral curvature, such as dorsal plication, fairy cuts, and corporal body grafting.
ICD-10: Different codes but identical guidelines

Accurate diagnosis coding essential for survival in the era of quality-based reimbursement

We have been helping urology groups prepare for the Oct. 1, 2015 switch to ICD-10 for diagnosis coding. We have audited many charts, looked at EHR templates, taught webinars and seminars to many urologists, and have more seminars scheduled. Of course, Physician Reimbursement Services is not the only group sounding the alarm on ICD-10 codes. Two of the common themes we see in advertising for ICD-10 training courses are the increased number of codes in ICD-10 and the increase in specificity the codes allow.

We agree with these general statements, which apply to the entire system. However, the realities of the U.S. health care system should be used to encourage every care provider to step away from the ledge, regroup, and take a more balanced approach to the transition. Are there going to be problems? Probably. But we would predict that the problems are going to initially be more about system glitches than inappropriate codes.

Comparing ICD-9 and ICD-10

Let’s look at one real example: coding for treatment of patients with cancer.

First, let’s take a look at current ICD-9 guidelines (first published in 2011) for diagnosis (Dx) coding as it relates to cancer. For the example, we will use bladder cancer, although many of these guidelines are general cancer guidelines and will apply to all cancer codes.

During ICD-9 or -10 training courses, you may have heard the directive to code what is known at the end of the encounter. In short, you are supposed to select the code for the symptom or diagnosis, which is documented in the record at the end of the service. Do not wait for the pathology report or other information to go back and report the diagnosis for an encounter or service provided.

We would predict that problems with ICD-10 are going to initially be more about system glitches than inappropriate codes.

ICD-10 carries more explicit instructions, but the instruction is clearly the same: “Each healthcare encounter should be coded to the level of certainty known for that encounter.”

Using our simplified bladder cancer example: A patient upon cystoscopy is noted to have one lesion 0.5 cm on the left lateral wall of the bladder; the lesion is biopsied and resected.

Dx known for the encounter:

- ICD-9: 239.4 Neoplasms of unspecified nature: Bladder
- ICD-10: D49.4 Neoplasm of unspecified behavior of bladder.

Typically, after the biopsy report is returned and the lesion is determined to be malignant, the patient is then scheduled for BCG treatment directed at the malignant neoplasm to ensure the cancer has been eradicated.

A typical note would read: Patient returns for BCG following resection of 0.5 cm malignant lesion of bladder wall. BCG instilled. Pt. tolerated the procedure well and return for repeat treatment in 3 months.

Dx known for the BCG encounter:

- ICD-9: 188.2 Malignant Neoplasm Of Bladder: Lateral Wall Of Urinary Bladder
- ICD-10: C67.2 Malignant neoplasm of lateral wall of bladder.

The Dx we actually see for many offices currently reporting this service with documentation such as this is:

- ICD-9: 188.9 Malignant Neoplasm Of Bladder: Bladder, Part Unspecified

In short, we already have specificity for many codes that we are not using to report the correct diagnosis. Most are paid using this diagnosis. As a further demonstration of the inaccuracy of this coding, here are the following instructions in both ICD-9 and ICD-10.

ICD-9/Chapter 2: Neoplasms (140-239)/General guidelines

a. Treatment directed at the malignancy

   If the treatment is directed at the malignancy, designate the malignancy as the principal diagnosis.

   The only exception to this guideline is if a patient admission/encounter is solely for the administration of chemotherapy, immunotherapy or radiation therapy, assign the appropriate V58.x code as the first-listed or Please see ICD-10, page 20

The information in this column is designed to be authoritative, and every effort has been made to ensure its accuracy at the time it was written. However, readers are encouraged to check with their individual carrier or private payers for updates and to confirm that this information conforms to their specific rules.
ICD-10
continued from page 19

principal diagnosis, and the diagnosis or problem for which the service is being performed as a secondary diagnosis.

ICD-10/Chapter 2:
Neoplasms (C00-D49)/General guidelines
d. Primary malignancy previously excised

The secondary site may be the principal or first-listed with the V10 code used as a secondary code.

ICD-10/Chapter 2:
Neoplasms (C00-D49)/General guidelines
a. Treatment directed at the malignancy

If the treatment is directed at the malignancy, designate the malignancy as the principal diagnosis.

The only exception to this guideline is if a patient admission/encounter is solely for the administration of chemotherapy, immunotherapy or radiation therapy, assign the appropriate Z51.-- code as the first-listed or principal diagnosis, and the diagnosis or problem for which the service is being performed as a secondary diagnosis.

Codes have changed, guidelines haven’t

Obviously, the codes themselves have changed, but the guidelines are identical. If all offices were to follow these guidelines and payers were restricting payment only to correctly diagnosed encounters, the following ICD-9 diagnoses would be reported (in appropriate order):

V58.12 Encounter For Other And Unspecified Procedures And Aftercare: Encounter For Chemotherapy And Immunotherapy For Neoplastic Conditions: Encounter For Antineoplastic Immunotherapy

188.2 Malignant Neoplasm Of Bladder: Lateral Wall Of Urinary Bladder

For ICD-10 Dx coding for BCG in treatment phase:

V58.12 Encounter For Antineoplastic Immunotherapy

C67.2 Malignant neoplasm of lateral wall of bladder

Once the patient has completed BCG treatment or is deemed in the patient record to be free of cancer and is moved to surveillance cystoscopy to monitor for recurrence, ICD-9 and ICD-10 provide the following guidelines for coding.

ICD-9/Chapter 2:
Neoplasms (140-239)/General guidelines
d. Primary malignancy previously excised

When a primary malignancy has been previously excised or eradicated from its site and there is no further treatment directed to that site and there is no evidence of any existing primary malignancy, a code from category Z85, Personal history of malignant neoplasm, should be used to indicate the former site of the malignancy. Any mention of extension, invasion, or metastasis to another site is coded as a secondary malignant neoplasm to that site. The secondary site may be the principal or first-listed with the Z85 code used as a secondary code.

Based on these guidelines, Dx coding for visits in which surveillance cystoscopy is performed and the results of the cystoscopy are negative or the bladder is noted to be clear should be as follows:

- ICD-10: Z86.51 Personal history of malignant neoplasm of bladder.

If there is a recurrence of bladder cancer that is verified and documented, services during treatment of the next occurrence would be coded to the appropriate malignant neoplasm of the bladder code until once again eradicated.

While this example does not cover all the nuances of coding for cancer in all organs or types of cancer, the general rules apply to other organs treated. We did not cover metastatic disease due to space; these scenarios are also governed similarly in both ICD-9 and ICD-10.

Conclusions

Look at how you are coding in your own practice and whether you are being paid for the services you provide. Consider as well that although ICD-10 has been used by the rest of the world for over a decade, the rest of the world does not use CPT for payment and does not use ICD coding to restrict or verify payment validity. In short, the data systems that are being used today to determine payment with ICD-9 in the U.S. will be the same data sets that will be used to determine payment using ICD-10, with the obvious use of crosswalks to ICD-10 codes.

Some have asked about other diagnosis codes for underlying patient conditions, fearful that the new system will require five or more diagnoses in order to process the claim. Again, we point back to ICD-9 and the current rules, which are similar to those in ICD-10. Are you having to submit five or more codes to get paid? Are you required to list all the underlying diseases to get paid for the treatment of a urology-specific problem? In most cases, the answer is no.

Will payer systems eventually become more sophisticated and be implemented to further restrict payment? Probably.

There is another path and we are on it. With the Physician Quality Reimbursement System, meaningful use, value-based modifier, the merit-based incentive payment system (soon), and a market shift to value-quality-based payment, the payers—including Medicare—can afford to allow poor coding in the straight fee-for-service world to continue in the short term. As the system moves beyond the pure fee-for-service world, you will be compared to your colleagues for cost-efficient care.

One easy place to start comparing quality is to look at those providers who can demonstrate results through Dx.

Following a Dx progression in which a patient is diagnosed with a lesion, cancer is identified and treated appropriately during the active treatment phase, followed actively in the aftercare phase and then declared as having a history of cancer is much more desirable to a patient who still has cancer.

We hope this article has provided at least a small amount of comfort in pointing out that the system change on Oct. 1, 2015 will not be the Armageddon that many have predicted.

However, you all know that PRS’s approach to coding is all about accuracy. Mistakes happen; correct them and move on. Ignorance, whether deliberate or not, will eventually catch up with you. We also look toward the future and see that accuracy in diagnosis coding must improve if you are going to survive in a reimbursement system based on quality.

We strongly recommend that you take the next few months to clean up your ICD-9 coding. We also recommend that you work toward making certain that you understand the rules you will be judged by under ICD-10. Learn the crosswalks and adjust them to accurately reflect what you do. You will also need to learn the new ICD-10 coding system. Update your templates and coding tools and make sure that your staff has access to knowledge, training, and tools that allow them to succeed in the tasks you have hired them to perform.

ICD-10 will be implemented. But do not panic. Take your time and learn the system correctly. Your future will depend on it.
The Oncotype DX® GPS refines risk stratification in men with clinically low-risk prostate cancer, leading to greater confidence in treatment decisions.

www.OncoTypeDX.com/prostate
Malpractice: How you can prevent a lawsuit

Improper performance of a procedure, error in diagnosis most common reasons for litigation

The most effective protection against the threat of malpractice litigation is also the least expensive.

“Show empathy, particularly in patients you are going to operate on. Take the extra time to explain the surgery and exactly what is going to be done. This will improve the doctor-patient communication and give the patient a better understanding of the procedure. Additionally, when you explain the procedure, you should use procedure-specific consents,” Christopher L. Coogan, MD, professor of urology at the Rush University Medical Center, Chicago, told Urology Times.

Informing patients of a procedure and the likelihood of its varied outcomes, as well as documenting the conversation, decreases both rate of suits as well as the likelihood of their succeeding, said Dr. Coogan, who chaired a 3-hour course on malpractice at the AUA annual meeting in New Orleans.

“Communication is the key to preventing a lawsuit,” he added.

Issue not well studied

Despite the impact a malpractice suit can have on a urologist’s practice, the issue does not appear to be well studied. Dr. Coogan noted two studies. One, a study of malpractice risks for urologists published in Urology (1998; 51:183-5) by George Kaplan, MD, of Children’s Hospital, San Diego, compared litigation frequency among urologists listed in Best Doctors in America with candidates for recertification by the American Board of Urology. It found some geographic variation in rates but concluded that there seemed to be no direct or inverse correlation between reputation and the incidence of lawsuits.

The second study mentioned by Dr. Coogan was conducted by C.J. Stimson, MD, JD, of Vanderbilt University Medical Center, Nashville, TN, and appeared in the Journal of Urology (2010; 183:1971-6). This study looked at the frequency of patient complaints against urologists as a surrogate for lawsuits and found that close to half (47%) of the physicians received no complaints, while 11% of the 268 urologists in the study drew half the complaints.

“Thus, not all doctors appear to face the same risk,” Dr. Coogan observed.

Two types of defensive responses

The possibility of litigation has evokes two common responses.

“There are two types of defensive (preventive) responses. The first is known as ‘assurance behavior,’ whereby a doctor will order additional tests to reduce their risk of being sued. Some studies have shown that up to 80% of all doctors may practice assurance medicine,” said Dr. Coogan.

“The second defensive tactic is known as avoidance behavior, in which doctors distance themselves from negative-risk patients and refer challenging procedures and difficult patients. These practices may occur in around 40% of doctors.”

As may be expected, the average costs (indemnity) associated with malpractice claims have risen, from $196,005 in 1988-1992 to $350,304 in 2008-2012, according to data presented by Dr. Coogan. One of the factors driving this increase is the rise in attorneys’ fees, which went from a little over $20,000 per case in 1989 to over $40,000 20 years later in 2009. The costs of expert witnesses were around $10,000 in 2009, as were associated expenses.

Joining Dr. Coogan at the podium for the course were David Sobel, MD, JD, of Urology Associates, P.C., Denver; Elizabeth Kavaler, MD, of New York Urological Associates, P.C., New York; and James W. Saxton, Esq, an attorney practicing with Saxton and Stump, LLC, Lancaster, PA.

Malpractice lessons learned: One doctor’s experience

By Jeffrey Bendix, MA

Edward Zurad, MD, knows first-hand what it’s like to go through a malpractice lawsuit. A solo family practitioner in a rural northeastern Pennsylvania county, Dr. Zurad also serves as medical director for several area companies.

In 1996, he found himself among four defendants in a medical malpractice lawsuit filed by an employee at one of the companies, who was experiencing chronic pain after falling from a stepladder. The suit, which also named the emergency department (ED) physician who first treated the employee, the hospital where the ED employee worked, and the radiologist, alleged that the pain resulted from a delayed diagnosis. All the defendants were acquitted following a 2-week jury trial in 2002.

In some respects, Dr. Zurad’s case was unusual, in that the plaintiff was not one of his regular patients, and the case went to trial rather than being settled out of court. But in other ways it was typical, starting with how long it took—6 years—to be resolved.

“Communication is the key to preventing a lawsuit,” he added.

Issue not well studied

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A 49-year-old Illinois man went to the emergency room in 2011 with what he believed was pain from a kidney stone. A computed tomography scan showed a large mass on the left kidney that was thought to be cancer.

A few weeks later, the patient underwent laparoscopic surgery to remove the left kidney. The urologist performing the operation was assisted by his partner, another urologist. The assistant held the camera so that the surgeon could see the relevant anatomy. Several hours into the operation, the assistant left the operating room to perform a vasectomy on a patient in his office on the hospital campus. During this time, a technician operated the camera.

After the assistant left the operating room, the surgeon encountered bleeding. He used a GIA stapler—with both stapling and cutting components—which was left in place to identify the source of the bleeding, and the surgeon asked the nurses to find another surgeon to help him. A general surgeon came from an adjacent operating room to assist. The stapling device was then removed from the cavity, and the first assistant surgeon returned to the operating room before the kidney was removed.

After surgery, the patient complained of pain in his legs and lacked a pulse and feeling in his legs. An arteriogram showed a dark mass within the aorta. He was then transferred to another hospital for exploratory surgery. A vascular surgeon discovered that the aorta had been cut in half and stapled to both sides. This cut off the blood flow to the spinal cord and legs.

This surgeon also found that the right renal arteries had been stapled and cut by a GIA stapler, which caused functional damage to the healthy right kidney. The patient is now paraplegic.

Once a jury sees the defendants pointing the finger at each other, they assume something must have been below the standard of care or they would not be blaming each other.

How can our clinical innovation save you money?

With the healthcare system facing cost pressures from all sides, we know that creating products that solve clinical problems is only half the battle. We need to be innovative by designing products that help you reduce costs. Whether by reducing necessary product, eliminating a procedural step, or freeing up some hands in the OR, our exclusive products for specialty urology can help you contain costs.
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Bone complications, or skeletal-related events (SREs), are defined as radiation to bone, pathologic fracture, surgery to bone, and spinal cord compression.

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XGEVA® is indicated for the prevention of skeletal-related events in patients with bone metastases from solid tumors.

XGEVA® is not indicated for the prevention of skeletal-related events in patients with multiple myeloma.

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IMPORTANT SAFETY INFORMATION

Hypocalcemia
• Pre-existing hypocalcemia must be corrected prior to initiating therapy with XGEVA®. XGEVA® can cause severe symptomatic hypocalcemia, and fatal cases have been reported. Monitor calcium levels and administer calcium, magnesium, and vitamin D as necessary. Monitor levels more frequently when XGEVA® is administered with other drugs that can also lower calcium levels. Advise patients to contact a healthcare professional for symptoms of hypocalcemia.

• An increased risk of hypocalcemia has been observed in clinical trials of patients with increasing renal dysfunction, most commonly with severe dysfunction (creatinine clearance less than 30 mL/minute and/or on dialysis), and with inadequate/no calcium supplementation. Monitor calcium levels and calcium and vitamin D intake.

Hypersensitivity
• XGEVA® is contraindicated in patients with known clinically significant hypersensitivity to XGEVA®, including anaphylaxis that has been reported with use of XGEVA®. Reactions may include hypotension, dyspnea, upper airway edema, lip swelling, rash, pruritus, and urticaria. If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue XGEVA® therapy permanently.

Drug Products with Same Active Ingredient
• Patients receiving XGEVA® should not take Prolia® (denosumab).

Osteonecrosis of the Jaw
• Osteonecrosis of the jaw (ONJ) can occur in patients receiving XGEVA®, manifesting as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain or slow healing of the mouth or jaw after dental surgery may also be manifestations of ONJ. In clinical trials in patients with osseous metastasis, the incidence of ONJ was higher with longer duration of exposure.

• Perform an oral examination and appropriate preventive dentistry prior to the initiation of XGEVA® and periodically during XGEVA® therapy. Advise patients regarding oral hygiene practices. Avoid invasive dental procedures during treatment with XGEVA®.

• Patients who are suspected of having or who develop ONJ while on XGEVA® should receive care by a dentist or an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition.

Atypical Subtrochanteric and Diaphyseal Femoral Fracture
• Atypical femoral fracture has been reported with XGEVA®. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution.

• Atypical femoral fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture. During XGEVA® treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Any patient who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of XGEVA® therapy should be considered, pending a risk/benefit assessment, on an individual basis.

Embryo-Fetal Toxicity
• XGEVA® can cause fetal harm when administered to a pregnant woman. Based on findings in animals, XGEVA® is expected to result in adverse reproductive effects.

• Advise females of reproductive potential to use highly effective contraception during therapy, and for at least 5 months after the last dose of XGEVA®. Apprise the patient of the potential hazard to a fetus if XGEVA® is used during pregnancy or if the patient becomes pregnant while patients are exposed to XGEVA®.

Adverse Reactions
• The most common adverse reactions in patients receiving XGEVA® with bone metastasis from solid tumors were fatigue/asthenia, hypophosphatemia, and nausea. The most common serious adverse reaction was dyspnea. The most common adverse reactions resulting in discontinuation were osteonecrosis and hypocalcemia.

Please see brief summary of Prescribing Information on the following page.


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www.XGEVA.com
INDICATIONS AND USAGE:
Bone Metastasis from Solid Tumors. Xgeva is indicated for the prevention of skeletal-related events in patients with bone metastases from solid tumors.

Important Limitation of Use. Xgeva is not indicated for the prevention of skeletal-related events in patients with multiple myeloma.

**DOSAGE AND ADMINISTRATION:**
Recommended Dosage. The recommended dose of Xgeva is 120 mg administered as a subcutaneous injection every 4 weeks in the upper arm, upper thigh, or abdomen. Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia.

Preparation and Administration. Visually inspect Xgeva vial for particulate matter and discoloration prior to administration. Xgeva is a clear, colorless to pale yellow solution that may contain trace amounts of white proteinaceous particles. Do not use if the solution is discolored or cloudy or if the vial contains many particles or foreign particulate matter. Prior to administration, Xgeva may be removed from the refrigerator and brought to room temperature (up to 25°C/77°F) by standing in the original container. This generally takes 15 to 30 minutes. Do not warm Xgeva in any other way. Use a 27-gauge needle to withdraw and inject the entire contents of the vial. Do not re-enter the vial. Discard vial after single-use or entry.

**CONTRAINDICATIONS:**
Hypocalcemia. Pre-existing hypocalcemia must be corrected prior to initiating therapy with Xgeva.

Hypersensitivity. Xgeva is contraindicated in patients with known clinically significant hypersensitivity to Xgeva.

**WARNINGS AND PRECAUTIONS:**
Drug Products with Same Active Ingredient. Xgeva includes the same active ingredient (denosumab) found in Prolia. Patients receiving Xgeva should not take Prolia.

Hypersensitivity. Clinically significant hypersensitivity including anaphylaxis has been reported with use of Xgeva. Reactions may include hypotension, dyspnea, upper airway edema, lip swelling, rash, pruritus, and urticaria. If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue Xgeva therapy permanently.

Hypocalcemia. Xgeva can cause severe symptomatic hypocalcemia. Severe hypocalcemia have been reported with use of Xgeva. Hypocalcemia has been reported with use of Xgeva. Severe hypocalcemia may occur during or shortly after the last dose of Xgeva. Discontinue Xgeva therapy in patients with severe hypocalcemia, pending a risk/benefit assessment, on an individual basis.

EMBRYO-FOetal TOXICITY: Xgeva can cause fetal harm when administered to a pregnant woman. Based on findings in animals, Xgeva is expected to result in adverse reproductive effects. In pregnant cynomolgus monkeys exposed to denosumab in cisternal injection of 4 mg/kg/day on gestation days 5 through 20, maternal hypocalcemia was observed. Pregnancy exposure and results from animal reproduction studies have not been established. Formula-fed infant exposure is not known.

**ADVERSE REACTIONS:**
The following adverse reactions are discussed below and elsewhere in the labeling:

- **Hypocalcemia**
- **Osteonecrosis of the Jaw**
- **Fracture**

**Clinical Trials Experience.** Because clinical trials are conducted under controlled conditions, adverse event rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in practice. The safety of Xgeva was evaluated in three randomized, double-blind, double-dummy trials in which a total of 2841 patients with bone metastasis from prostate cancer, breast cancer, or other solid tumors, or lytic bony lesions from multiple myeloma received at least one dose of Xgeva. In Trials 1, 2, and 3, patients were randomized to receive either 120 mg of Xgeva every 4 weeks (median overall exposure of 14.6 months) or 8 mg/month of zoledronic acid (median exposure of 12.0 months; range 0.1 – 40.5) and 1.3% of patients in the zoledronic acid group. The trials in patients with breast (Trial 1) or prostate (Trial 3) cancer included an Xgeva open label extension treatment phase where patients were offered Xgeva 120 mg once every 4 weeks (median overall exposure of 14.9 months; range 0.1 – 62.2). The patient-year adjusted incidence of confirmed ONJ was 1.1% during the first year of treatment and 4.1% thereafter. The median time to ONJ was 20.6 months (range 4 – 53).

Atypical Subtrochanteric and Diaphyseal Femoral Fracture. Atypical femoral fractures have been reported with use of Xgeva.

Postmarketing Experience. Because postmarketing reports are volunteered from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following adverse reactions have been identified during post approval use of Xgeva:

- **Hypocalcemia:**
- **Osteonecrosis of the Jaw:**
- **Fracture:**
- **Hypersensitivity:**
- **Musculoskeletal pain:**

Immunogenicity. As with all therapeutic proteins, there is potential for immunogenicity. Using an

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**Table 1. Per-patient Incidence of Selected Adverse Reactions of Any Severity (Trials 1, 2, and 3)**

<table>
<thead>
<tr>
<th>Body System</th>
<th>Xgeva n = 2841</th>
<th>Zoledronic Acid n = 2836</th>
</tr>
</thead>
<tbody>
<tr>
<td>GASTROINTESTINAL</td>
<td>Nausea</td>
<td>31</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>GENERAL</td>
<td>Fatigue/ Asthenia</td>
<td>45</td>
</tr>
<tr>
<td>INVESTIGATIONS</td>
<td>Hypocalcinemia*</td>
<td>18</td>
</tr>
<tr>
<td>Hypothyrotemia</td>
<td>32</td>
<td>20</td>
</tr>
<tr>
<td>NEUROLOGICAL</td>
<td>Headache</td>
<td>13</td>
</tr>
<tr>
<td>RESPIRATORY</td>
<td>Dyspnea</td>
<td>21</td>
</tr>
<tr>
<td>Cough</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

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Eighty-five percent were White, 5% Hispanic/Latino, 6% Asian, and 3% Black. The median age was 63 years (range: 18 – 93). Seventy-five percent of patients who received Xgeva received concomitant chemotherapy.

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**Immunogenicity.** As with all therapeutic proteins, there is potential for immunogenicity. Using an
various anticancer treatments affected denosumab similarly in patients with and without prior intravenous trials in patients with breast cancer metastatic to trials have been conducted with Xgeva. In clinical DRUG INTERACTIONS: products may be misleading. to denosumab with the incidence of antibodies to other disease. For these reasons, comparison of antibodies collection, concomitant medications, and underlying assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of antibodies to denosumab with the incidence of antibodies to other products may be misleading.

**DRUG INTERACTIONS:** No formal drug-drug interaction trials have been conducted with Xgeva. In clinical trials in patients with breast cancer metastatic to bone, Xgeva was administered in combination with standard anticanter treatment. Serum denosumab concentrations at 1 and 3 months and reductions in the bone turnover marker uNTx/Cr (urinary N-terminal telopeptide corrected for creatinine) at 3 months were similar in patients with and without prior intravenous bisphosphonate therapy. There was no evidence that various cancer treatments affected denosumab systemic exposure and pharmacodynamic effect. Serum denosumab concentrations at 1 and 3 months were not altered by concomitant chemotherapy and/or hormone therapy. The median reduction in uNTx/Cr from baseline to month 3 was similar between patients receiving concomitant chemotherapy and/or hormone therapy.

**USE IN SPECIFIC POPULATIONS:**

**Pregnancy:** Category D. Risk Summary: Xgeva can cause fetal harm when administered to a pregnant woman based on findings in animals. In utero denosumab exposure in cynomolgus monkeys resulted in increased fetal loss, stillbirths, and postnatal mortality, along with evidence of absent lymph nodes, abnormal bone growth and decreased neonatal growth. There are no adequate and well-controlled studies with Xgeva in pregnant women. Women who should be advised not to become pregnant when taking Xgeva. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.Women who might become pregnant during Xgeva treatment are encouraged to enroll in Amgen’s Pregnancy Surveillance Program. Patients or their physicians should call 1-800-777-AMGEN (1-800-777-6436) to enroll.

**Clinical Considerations:** The effects of Xgeva are likely to be greater during the second and third trimesters of pregnancy. Monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester. If the patient becomes pregnant during Xgeva therapy, consider the risks and benefits in continuing or discontinuing treatment with Xgeva.

**Animal Data:** The effects of denosumab on prenatal development have been studied in both cynomolgus monkeys and genetically engineered mice in which RANKL expression was turned off by gene removal (a “knockout mouse”). In cynomolgus monkeys dosed subcutaneously with denosumab throughout pregnancy at a pharmacologically active dose, there was increased fetal loss during gestation, stillbirths, and postnatal mortality. Other findings in offspring included absence of axillary, inguinal, mandibular, and mesenteric lymph nodes; abnormal bone growth, reduced bone strength, reduced hematopoiesis, dental dysplasia and tooth malalignment; and decreased neonatal growth. At birth out to one month of age, infants had measurable blood levels of denosumab (22-61% of dosing levels). Following a recovery period from birth out to 6 months of age, the effects on bone quality and strength returned to normal; there were no adverse effects on tooth eruption, though dental dysplasia was still apparent; auxiliary and inguinal lymph nodes remained absent, while mandibular and mesenteric lymph nodes were present, though small; and minimal to moderate mineralization in multiple tissues was seen in one recovery animal. There was no evidence of maternal harm prior to labor; adverse maternal effects occurred infrequently during labor. Maternal mammary gland development was normal. There was no evidence of a dose-related adverse effect (90% of incidence level) established for this study because only one dose of 50 mg/kg was evaluated. In RANKL knockout mice, absence of RANKL (the target of denosumab) also caused fetal lymph node agenesis and led to postnatal impairment of dentition and bone growth. Pregnant RANKL knockout mice showed altered maturation of the maternal mammary gland, leading to impaired lactation.

**Nursing Mothers:** It is not known whether Xgeva is excreted into human milk. Measurable concentrations of denosumab were present in the maternal milk of cynomolgus monkeys up to 1 month after the last dose of denosumab (≤ 0.5% milk:serum ratio). Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Xgeva, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. Maternal exposure to Xgeva during pregnancy may impair mammary gland development and lactation based on findings in animals. In utero denosumab administration of animal studies in pregnant mice lacking the RANK/RANKL signaling pathway that have shown altered maturation of the maternal mammary gland, leading to impaired lactation and postnatal impairment of dentition. However, in cynomolgus monkeys treated with denosumab throughout pregnancy, maternal mammary gland development was normal, with no impaired lactation. Mammary gland histopathology at 6 months of age was normal in female offspring exposed to denosumab in utero; however, development and lactation have not been fully evaluated.

**Pediatric Use:** Xgeva is not recommended in pediatric patients. The safety and effectiveness of Xgeva in pediatric patients have not been established. Treatment with Xgeva may impair bone growth in children with open growth plates and may inhibit eruption of dentition. In adolescent primates treated with denosumab at doses 5 and 25 times (10 and 50 mg/kg dose) higher than the recommended human dose of 120 mg administered once every 4 weeks, based on body weight (mg/kg), had abnormal growth plates, considered to be consistent with the pharmacological activity of denosumab. Cynomolgus monkeys exposed in utero to denosumab exhibited bone abnormalities, reduced hematopoiesis, tooth malalignment, decreased neonatal growth, and an absence of axillary, inguinal, mandibular, and mesenteric lymph nodes. Some bone abnormalities recovered once exposure was ceased following birth; however, axillary and inguinal lymph nodes remained absent 6 months post-birth.

**Geriatric Use:** Of patients who received Xgeva in Trials 1, 2, and 3, 1260 (44%) were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients. 

**Renal Impairment:** Two clinical trials were conducted in patients without cancer and with varying degrees of renal function. In one study, patients (N=50) with varying degrees of renal function (ranging from normal through end-stage renal disease requiring dialysis) received a single 60 mg subcutaneous dose of denosumab. In a second study, patients (N=32) with severe renal dysfunction (creatinine clearance less than 30 mL/min and/or dialysis) were given two 10 mg subcutaneous doses of denosumab. In both studies, greater risk of developing hypocalcemia was observed with increasing renal impairment, and with inadequate/no calcium supplementation. Hypocalcemia was mild to moderate in severity in 46% of patients. Monitor calcium levels and, calcium and vitamin D intake.

**Females and Males of Reproductive Potential.**

**Contraception** Females: Counsel patients on pregnancy planning and prevention. Advise females of reproductive potential to use effective contraception during treatment, and for at least 5 months after the last dose of Xgeva. Advise patients to contact their healthcare provider if they become pregnant, or if a pregnancy is suspected, during treatment or within 5 months after the last dose of Xgeva. Males: The extent to which denosumab is present in seminal fluid is unknown. There is potential for female exposure to denosumab when a male treated with Xgeva has unprotected sexual intercourse with a pregnant partner. Advise males of this potential risk.

**OVERDOSAGE:** There is no experience with overdosage of Xgeva.

**HOW SUPPLIED/STORAGE AND HANDLING:** Xgeva is supplied in a single-use vial. Store Xgeva in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze. Once removed from the refrigerator, Xgeva must not be exposed to temperatures above 25°C (77°F) or direct light and must be used within 14 days. Discard Xgeva if not used within the 14 days. Do not use Xgeva after the expiry date printed on the label. Protect Xgeva from direct light and heat. Avoid vigorous shaking of Xgeva.

**PATIENT COUNSELING INFORMATION:**

**Avoiding therapy with Xgeva if a serious allergic reaction occurred with prior Xgeva or Prolia therapy**

**Proper oral hygiene and routine dental care**

**Informing their dentist that they are receiving Xgeva**

**Avoiding invasive dental procedures during treatment with Xgeva**

**The use of highly effective contraception during and for at least 5 months after treatment with Xgeva for females of reproductive potential**

Advise patients that denosumab is also marketed as Prolia®. Patients should inform their healthcare provider if they are taking Prolia.

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mCRPC advances come with choices, challenges

New treatments require familiarity with clinical guidelines, documentation of performance status, and costs

The last 5 years have seen dramatic changes in the choices available to urologists for treatment of advanced prostate cancer. With this problem have been traditionally treated in a urology practice with a combination of injectable gonadotropin-releasing hormone agonists/antagonists and oral antiandrogens until they progressed—and then, if their performance status permitted, they were referred to a medical oncologist for consideration of cytotoxic chemotherapy. The FDA approval of immunotherapy (sipuleucil-T [Provenge]) in 2010, denosumab (XGEVA) in 2010, abiraterone acetate (ZYTIGA) in 2011, enzalutamide (XTANDI) in 2012, and radionuclide therapy (radium-223 [XOFIGO]) in 2013 has changed the treatment landscape for these patients and the urologists who manage them.

In this article, I examine some of the practice-related implications of this rapid change in the management of patients with advanced prostate cancer.

Knowledge of guidelines important

The AUA first published its guidelines on castration-resistant prostate cancer in May 2013, and classified the recommendations based upon a matrix of metastatic status, symptoms, performance status, and prior chemotherapy with docetaxel (Taxotere). Grouping patients into categories (index patients), the guidelines offer therapy options based on these criteria and some evidence-based clarification of the decision-making process.

Long a mainstay of the medical oncologist’s lexicon, performance status is less commonly documented in the medical record of a urology practice.

The National Comprehensive Cancer Network (NCCN) guidelines on advanced prostate cancer closely mirror the AUA guidelines. Urologists may wish to familiarize themselves with NCCN guidelines, as they are more detailed and used by medical oncologists. Patients do not always progress in an orderly fashion through identifiable categories, but the guidelines offer an important framework for thinking about castration-resistant disease.

The decision-making process and complexity of managing these patients highlights the importance of identifying patients who are progressing based on clinical data like PSA kinetics and carefully documenting performance status and symptoms. While there are many tools available to measure performance status, the two most commonly used to assess functional status are the Karnofsky performance status and the Eastern Cooperative Oncology Group scales.

Long a mainstay of the medical oncologist’s lexicon, performance status is less commonly documented in the medical record of a urology practice. Commercial electronic health record systems may not include a convenient way to capture this information in a structured manner. The documentation of symptoms due to bony or visceral metastatic disease may be even more problematic.

Finally, the new array of therapeutic choices available to the urologist may introduce a new and lower threshold for ordering diagnostic studies to assess metastatic disease and bone health.

Urologists who have been entering “data”

LEGAL PERSPECTIVE: One of the most damaging scenarios to the defense in medical malpractice cases is that of dueling defendants. The strategy in which each defendant is trying to get himself off the hook by blaming the other is rarely successful, and most often, these cases will settle. Once a jury sees the defendants pointing the finger at each other, they assume something must have been below the standard of care or they would not be blaming each other. Even if there is no care below the standard in a particular case, the defense attorney will usually not want the dueling defendants in front of the jury and chance a large award because of the finger pointing.

IVP blamed for diminished kidney function

A 56-year-old Virginia man had suffered from diabetes for many years and had limited kidney function as a result. An intravenous pyelogram was ordered by his urologist and performed by a radiologist using contrast dye to assess kidney function. Shortly thereafter, he was placed on dialysis.

The patient sued the radiologist after the IVP, claiming it caused even more diminished function in his kidneys, necessitating the dialysis until he received a kidney transplant in 2008. He claimed that the IVP test was not necessary or should have been done without contrast dye, and that a less invasive test could have been done to assess kidney function; a creatinine level would have sufficed.

The radiologist argued the IVP was an appropriate test, that the non-ionic contrast medium was used, and this medium was not the cause of any further loss of kidney function. The matter was first tried in 2007, and a defense verdict was returned. A new trial was granted, and this second trial also resulted in a defense verdict. UT

Nephrectomy

Continued from page 23

Paraplegic and uses a wheelchair. He also requires kidney dialysis treatment three times per week.

In the lawsuit that followed this incident, the patient claimed negligence by the hospital and all surgeons involved in the operation, alleging that their failure to inspect the anatomy and ensure proper function and blood flow prior to closing the surgical site caused his debilitating injuries.

The main surgeon denied causing the stapling injuries and claimed that the general surgeon who came in to help was the only other person who used the stapler during the operation. The assistant surgeon maintained that he was not in the operating room when the stapling device was used. The general surgeon was dismissed from the case, and a $30 million settlement was then reached.

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into their EHR system are now beginning to ask whether the information can be “mined” for various purposes, including identifying gaps in care (vis a vis guidelines) or looking across a large practice for opportunities to offer patients one of these newer therapies. Clearly, this capability will depend in part on the quality and quantity of documentation, including symptoms, performance status, and metastatic status.

Revenue opportunities
More choices for urologists and their patients may mean a healthier bottom line for the practice. In addition to preventive therapies like denosumab that can easily be offered in a urology office, practices are now offering infusion centers (sipuleucil-T), comprehensive bone health programs (including bone mass density measurement), in-office dispensing (oral agents), or even comprehensive cancer centers that include chemotherapy administration. Some of these therapies are expensive, but still profitable in a well-managed practice.

The next generation of prostate cancer care will probably include an active population health (proactive) management paradigm instead of the current office visit-based care. Urology practices will need to be able to identify patients who have gaps in care, or are new candidates for targeted care, outside of the exam room and in a model that depends on reliable clinical documentation, measurement, clinical analytics, and quality improvement.

Bottom line: There are more opportunities for urologists to continue to manage even the most advanced prostate cancer patients in their practice, but those opportunities are accompanied by needs for increased attention to familiarity with complex guidelines, improved clinical documentation, and the costs of care.

MCRPC
continued from page 28

More choices for urologists and their patients may mean a healthier bottom line for the practice.
IRA beneficiaries: Know who receives what

Rules of inheritance differ according to whether beneficiary was spouse of deceased

Q How does the beneficiary designation of an IRA impact future distributions?

A Individual retirement accounts (IRAs) generally represent most physicians’ largest financial asset. With this in mind, it only makes sense to ensure that retirement account beneficiary decisions are carefully made. While many institutions provide custody services for traditional IRA assets, the onus is on the IRA owner to make the ultimate beneficiary decision.

Unfortunately, many physicians don’t take the time to understand and personally individualize the beneficiary language within the agreement to meet their specific objectives. Understanding the impact that the beneficiary designation has on the payout of the account after the IRA owner dies is a critical element of the planning process.

From the standpoint of those who inherit a traditional IRA (as opposed to a Roth IRA), it’s important to have an understanding of the unique rules associated with the process, which is different for spousal beneficiaries and non-spouse beneficiaries.

If you are the sole beneficiary of your spouse’s traditional IRA, you may choose to treat that IRA as your own. This means you can contribute to the IRA if you are eligible to do so, and, if you are younger than 70½, you do not have to take required minimum distributions (RMDs). RMDs are generally required after reaching age 70½. As an alternative, you may leave the IRA in your spouse’s name with you as the beneficiary. If your deceased spouse died after age 70½, you generally must base subsequent RMDs on the longer of your single life expectancy or the deceased’s life expectancy. Otherwise, distributions may be based on your single life expectancy or the account must be totally liquidated in 5 years. Another possible option is to roll over the inherited IRA assets into your own IRA. The rollover is exempt from current tax liability if completed within 60 days.

If, on the other hand, you inherit an IRA from someone other than your spouse, you cannot treat the IRA as your own. Thus, you are not allowed to make subsequent contributions to the inherited IRA, nor can you roll over the funds to your own IRA. You must begin taking RMDs subject to the rules for IRA beneficiaries. Distributions from an inherited IRA are taxed at ordinary income tax rates. If you fail to take an RMD, you must pay a penalty tax equal to 50% of the required amount of the distribution.

Typically, married IRA owners will name their spouse as beneficiary, due to the many advantages of doing so, while either not naming or giving very little consideration to whom the contingent beneficiary should be. Those who do name a contingent beneficiary often name their children. Caution does need to be exercised in the event that one of the named children dies prior to the IRA owner. Typically, the deceased child’s portion of the inheritance would go to the other living children, as opposed to the deceased child’s family. This may indeed be your objective.

However, if your intention is to have your child’s portion pass through to their heirs, be sure to add the line: “to my descendants per stirpes.” The Latin term “per stirpes” means “by right of the deceased.” This specific legal terminology will ensure that if the beneficiary child dies, his/her descendants get the full share.

There are many IRA intricacies and nuances that should be addressed proactively to ensure you are maximizing both income tax and estate tax planning opportunities. Be sure to consult with your tax or financial adviser to ensure your IRA is structured properly now in order to avoid surprises or problems in the future.

Q How do I leave assets to my spouse, who is not a U.S. citizen, and still minimize estate taxation?

A In general, a marital deduction is not available for a transfer to a surviving spouse who is not a U.S. citizen unless the transfer is to a qualified domestic trust (QDOT) for which the executor has made an election. A QDOT must qualify for the marital deduction as well as meet the following requirements:

- At least one trustee of the QDOT must be a U.S. citizen or a domestic corporation.
- No distribution (other than a distribution of income) may be made from the trust unless that trustee has the right to withhold any additional gift or estate tax imposed on the trust.

Additionally, estate tax is due on any property remaining in the QDOT upon death of the surviving spouse (or at the time the trust ceases to qualify as a QDOT, if earlier).

Financial Tips

- The process of inheriting an IRA is different for spousal beneficiaries and non-spouse beneficiaries.
- If you are the sole beneficiary of your spouse’s traditional IRA, you may choose to treat that IRA as your own, meaning you can contribute to the IRA if you are eligible to do so, and, if you are younger than 70½, you do not have to take required minimum distributions.
- If you name a child as the contingent beneficiary of your IRA, be sure to determine who will inherit the IRA should the child pre-decease you.
- In general, a marital deduction is not available for a transfer to a surviving spouse who is not a U.S. citizen unless the transfer is to a qualified domestic trust for which the executor has made an election.

Money Matters

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

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

Send us your questions

Send your questions about estate planning, retirement, and investing to Joel M. Blau, CFP, c/o Urology Times, at UT@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.
The world’s smallest Digital Flexible URS
Combining optimal image quality and unrivaled access
“Telemedicine is probably the fastest growing component of health care delivery in the world right now. It is being used in some form or other in every major hospital in the United States. It’s starting to be used outside the hospital in clinics, even in homes and where people work,” said Jonathan Linkous, CEO of the American Telemedicine Association. “There are applications in urology. I think that’s an area that is still relatively small in growth, but it is coming along.”

Telemedicine is the use of medical information exchanged from one site to another via electronic communications to improve a patient’s clinical health status, according to the American Telemedicine Association.

Among the biggest areas for telemedicine are radiology, mental health, and critical care. One example of telemedicine’s muscle: about 11% of all intensive care unit beds in the country are now monitored, at least in part, by intensivists using telemedicine, according to Linkous.

“Specialty areas like urology have been growing because mid-sized hospitals, even some large hospitals, cannot afford to have urologists on site 24-7, but using this technology, now they can,” he said.

Documented cost savings and greater broadband availability are among the factors fueling telemedicine’s growth, according to Linkous.

“In the VA, telehealth is estimated to have saved nearly $2,000 per patient, per year. Home telehealth has led to a 35% reduction in hospital admissions, and mental health telehealth use has reduced inpatient mental health bed-days by 38%,” said Jeremy B. Shelton, MD, MSHS, a urologist and physician informatics specialist at the VA Greater Los Angeles Healthcare System and member of the UCLA urology faculty. “In our experience, telehealth has increased urology consult volume by 11% among rural patients, suggesting improved access to care. We also found that veterans had significant

Please see TELEMEDICINE, page 34

Tackling telemedicine one step at a time

Urologists interested in using telemedicine for patient care should do so with their eyes wide open, according to Stephen Canon, MD. Dr. Canon, Jonathan Linkous of the American Telemedicine Association, and Peter N. Bretan, Jr., MD, recommend urologists take these steps before committing to a telemedicine approach.

Step one
Understand the laws and regulations that impact telemedicine in your state.

While some states embrace telemedicine, others do not. The American Telemedicine Association offers two free and up-to-date state-by-state report cards on telemedicine. One is a gap analysis on coverage and reimbursement; the other focuses on physician practice standards and licensure. (For links to this and other resources discussed in this article, please see www.urologytimes.com/telemedicine-resources.)

Step two
Make sure you have access to a telemedicine technology and system infrastructure.

“It’s very important to protect privacy, but there isn’t a HIPAA-compliant technology. It’s a process,” Linkous said. “The technology is pretty ubiquitous, but if you’re providing care that is directly used to diagnose or treat a patient, then of course, you’ll have to use something that is approved by the FDA. Other than that, it’s pretty wide open. Interactive video is used quite often. It could be something simple that’s computer based or something complicated, like a private network. It really depends on the applications.”

Dr. Bretan provides telemedicine care from his laptop, by controlling an onsite robot. He says the robots, which actually go into patients’ rooms, are at many hospitals that don’t have access to local specialists. A video, “The Robot Will See You Now,” explains the process.

In Arkansas, Dr. Canon has access to the Antenatal and Neonatal Guidelines Education and Learning System (ANGELS), a consultative service for family practitioners, obstetricians, pediatricians, and neonatologists in the state. Pediatric urologists at Arkansas Children’s Hospital are regularly consulted for cases of prenatal hydronephrosis and other conditions.

Step three
Understand how to bill for telemedicine.

States may select from a variety of HCPCS codes (T1014 and Q3014), CPT codes, and modifiers (GT, U1-UD) in order to identify, track, and reimburse for telemedicine services, according to the Medicaid website.

“Billing for telemedicine primarily involved the addition of a GT modifier to the initial or follow-up visits, which are used every day by urologists,” Dr. Canon said. The American Telemedicine Association offers a reimbursement course.

Step four
Test the telemedicine waters.

“It’s a little bit of a shock to the infrastructure when you have a patient that is mixed in the schedule that is not going to be there in person, in the middle of a full day of clinic patients,” Dr. Canon said.

One tip: To better determine if they could and would use telemedicine to care for patients, Dr. Canon and colleagues tested the use of the technology for care during the 90-day global period, so billing was out of the equation.
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TELEMEDICINE
continued from page 32

travel saving through use of telehealth.”

Challenges to widespread telemedicine delivery are dwindling; however, hurdles remain.

Reimbursement for telemedicine is not the challenge it used to be, but it’s still a challenge, according to Linkous.

“If you look down the list of how things are paid for, private insurance and employers tend to do the best in reimbursing for telemedicine. There’s still some holdout, but it has become less and less. Forty to 45 states reimburse for at least part, if not all, of telemedicine under Medicaid. Medicare is the worst for telemedicine. It only covers patients in rural areas,” Linkous said.

“There isn’t enough business at the hospitals to keep urologists solvent. But, if I can cover them instantaneously with telemedicine, I can capture the care and keep patients local.”
PETER N. BRETN, JR., MD

Policy-based hurdles remain in some states, according to Dr. Shelton.

“Currently, telehealth regulation differs state by state. For example, some states ban initial visits through telehealth. Physician licensing is another barrier to delivering telehealth across state lines,” Dr. Shelton said.

Telemedicine rules and regulations can be complex. For example, if you’re a urologist in Florida and are using telemedicine to care for a patient in Alabama, you have to be licensed in both states. And, you have to follow the practice standards that are set by the medical boards in both states.

If the patient is in a hospital, you’ll have to be credentialed and privileged in that hospital, according to Linkous.

A good fit for the specialty
Telemedicine does not replace in-person care, according to Dr. Bretan. Rather, it is an adjunct to urologic care. The good news for urologists, he said, is that urology is a telemedicine-friendly specialty. Urologists often do not have to be there, physically, to care for patients. One reason for that is many urologic patients don’t come in through the emergency room with true emergencies.

“There’s really only one urologic emergency: torsion of the testicles. That doesn’t happen that often,” Dr. Bretan said.

Even when urologic emergencies do occur at a far-away hospital, Dr. Bretan can see and evaluate the patient acutely using a robotic telemedicine system. In some cases, he communicates with the emergency room physician that the patient needs to be stabilized and transported to another hospital with round-the-clock interventional radiology and other capabilities. In other cases, he works with the local staff to stabilize the patient and ready that person for surgery within 48 hours, giving Dr. Bretan time for the commute.

“I have to be ultra-flexible with my plans if I have to do surgery within 48 hours or so. But, it usually can wait much longer,” he said.

Specific uses
Telemedicine provides timely access to care for patients in rural areas, for indigent and prison care, as well as in urban areas, where access to a hospital might be limited because of traffic, according to Dr. Bretan. (For examples of telemedicine’s applicability in urban and suburban areas, see “Telemedicine’s use may expand beyond rural settings,” page 36.)

Practical uses for telehealth in urology include disease diagnosis and management, including some preoperative and postoperative visits; remote rounding; second opinions; and, possibly, remote surgery, according to Dr. Shelton.

“As a proof of principle, robotic surgery has been performed remotely,” Dr. Shelton said.

Stephen Canon, MD, chief of pediatric urology at Arkansas Children’s Hospital and associate professor in urology at the University of Arkansas for Medical Sciences, Little Rock, uses telemedicine as an adjunct to care in three areas: the delivery of postoperative care, specialty care when he can’t reach patients in remote locations, and some prenatal consultations.

Dr. Canon and colleagues published a study on their initial use of telemedicine for postoperative care in pediatric surgical patients (J Telemed Telecare 2014; 20:427-30). The study supports the use of telemedicine for the postoperative care of children who have had urologic surgery, saving on travel and time.

Dr. Canon, who regularly travels by plane to provide specialty care in remote Arkansas locations, uses telemedicine when weather grounds air travel. He also uses the technology when evaluating pregnant mothers with prenatal fetal urologic abnormalities. This helps when patients who might be 32 or 36 weeks into their pregnancies would have to travel far to get to the Children’s Hospital, he said.

Pediatric urologists, including Dr. Canon, and obstetricians at the University of Arkansas presented their findings in a poster session on

Please see TELEMEDICINE, page 38

“In our experience, telehealth has increased urology consult volume by 11% among rural patients, suggesting improved access to care.”

JEREMY B. SHELTON, MD, MSHS

“In the U.S., we spend too much on health care, and we have to somehow lower the cost and maintain or improve the quality. In order to do that, we’re going to have to use technology.”

STEPHEN CANON, MD

Guidelines for telemedicine practice

- The American Medical Association outlines its policy for safeguards and standards necessary for proper use of telemedicine (http://ow.ly/NM35o).

Technology

PETER N. BRETN, JR., MD

2014; 20:427-30). The study

JUNE 2015

Urology Times

JEREMY B. SHELTON, MD, MSHS

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Telemedicine has applications beyond care delivery to rural and underserved areas. Urologist Aaron Spitz, MD, is spearheading an effort in California to bring tele-urology to hospitals in Orange County and beyond. He says there’s a need in urban and suburban America to streamline access to urologists in emergency medicine and urgent care, and telemedicine is one solution.

Dr. Spitz is a partner in Orange County Urology Associates, Laguna Hills, CA, and is assistant clinical professor of urology at the University of California, Irvine. He and colleagues in orthopedics have joined to launch telemedicine services at two local hospitals and an urgent care center. The hospitals already have the infrastructure, including RP-VITA robots (In Touch Health), which they use in neurology, pediatric surgery, and psychiatry.

Urology and orthopedic surgery will be the first specialties to provide telemedicine evaluation in these facilities’ emergency rooms and in the urgent care setting. Dr. Spitz plans to expand telemedicine services to other hospitals after this initial launch.

We asked Dr. Spitz, who presented on the topic at the Practice Management Conference during the AUA annual meeting in New Orleans, to share his insight with Urology Times.

Overcoming workflow obstacles

**UT:** How might telemedicine apply to urology practice in urban and suburban areas?

**Dr. Spitz:** There are workflow obstacles for surgical subspecialists and patients in urban and suburban settings.

Most hospitals do not have in-house urologists. When a patient presents to the emergency room, requiring a urologist consultation, the urologist would typically have to leave his office and travel to that ER to see the patient. In most cases, that will not occur until the urologist has completed his office work; so, it might be during his lunch or after the end of his workday. There are other potential obstacles to timely care of the patient, including traffic.

As a result, the patient and the emergency room doctor or admitting hospitalist will have to wait potentially several hours or all day to receive an evaluation and a disposition as to what the next treatment steps will be.

**UT:** How does telemedicine, potentially, solve the problem?

**Dr. Spitz:** I can actually receive all the same data—x-ray, CT scan, vital signs, blood and urine test results, input and output of fluids—that I would if I physically went to the hospital because all the data is now in the electronic medical record. The audiovisual platform allows me to physically see the patient and the patient can see me. With an assistant at the patient’s bedside, which may be the doctor, a nurse, a physician assistant, or nurse practitioner, although I can’t touch the patient with my own hands, I can observe the exam, the patient’s reaction to it, and the description of it. I can ask questions and speak to the patient and family.

In many cases, all that will be sufficient for me to do the patient evaluation, as well as the disposition and obtain an informed consent for a procedure, if necessary. For all of that, can happen in the same amount of time it would take me if I were physically there, which typically is 15 minutes. And I can insert that 15-minute disruption into my office workflow, with a minor amount of delay.

If the patient requires surgery, it can be scheduled to occur as soon as I’m available, versus only starting the scheduling process after I’ve physically seen the patient. On the other hand, if the patient needs an intervention from another service after the consultation because I’ve determined that it’s not necessarily a urologic condition, the process of bringing in other services has not been unnecessarily delayed.

There’s one other scenario. It may be the case right after the doctor has evaluated the patient with all the tools—the robot, the EMR, etc.—that the urologist decides he physically needs to see that patient to complete the evaluation before making recommendations. At that stage, the patient will have to wait for the urologist to arrive; however, there is at least a doctor-patient relationship established. There will likely be some instructions the doctor can act on, such as if the patient has to be admitted or not. So, even if the full evaluation cannot be accomplished tele-medically, the part of the interaction that it did accomplish is still valuable.

**UT:** What is telemedicine’s application in urgent care?

**Dr. Spitz:** Currently, patients who are evaluated and treated in an urgent care setting are not able to be evaluated and treated for urologic conditions. Patients typically are instructed that they will have to follow up with their primary care doctor to receive a referral to a urologist. Occasionally, they’re told to go directly to a urologist, but it will have to be a referred urologist because there is no in-house urologist available in the urgent care facility.

With telemedicine, if the patient has a urologic condition that is amenable to telemedicine evaluation, that patient can receive the evaluation from a urologic physician, without having to go through one or two more steps.

An example in urgent care setting

**UT:** Can you give readers an example or two of what might occur in the urgent care setting?

**Dr. Spitz:** A patient may present to an urgent care clinic with a kidney stone. The urgent care clinic that I’m going to be working with has CT scan, x-ray, and ultrasound, as well as blood and urine diagnostic testing.

If the patient presents with symptoms of kidney stone, a CT scan can be obtained that confirms the diagnosis. Blood and urine tests can be obtained that notify me if the patient has signs of kidney impairment or infection.

Let’s say the patient has a kidney stone that is not infected and is not impairing his kidney function; the stone is of a certain size and location that will not pass spontaneously; and his pain can be controlled with oral pain medication. That patient can be informed with confidence of his condition. We can start treating his pain, and we can get underway with setting up a time for a kidney stone treatment. The patient can follow up with me, in-person, subsequently. But the scheduling of the procedure will all be underway.

Without telemedicine, the patient might be told that he has a kidney stone and he needs to see a urologist. The wait time to see the urologist might be 3 to 6 weeks. Once the urologist sees him for the first time, initiating the scheduling process might result in a further delay.

The whole workflow and care of that patient is radically expedited because of telemedicine availability in urology.
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TELEMEDICINE

continued from page 34

the technology’s use in prenatal fetal urologic abnormalities. “Our case series demonstrates the effectiveness of this process, by allowing patients who might otherwise have not been able to travel for subspecialty consultation, an opportunity to receive prenatal consultation,” according to the poster. “Telemedicine also allowed patients to deliver locally with the reassurance of established postpartum follow up and avoid the costs of unnecessary prenatal maternal transports. We believe that telemedicine is an effective tool for prenatal consultation with many potential benefits for the patient and healthcare team.”

In addition to good outcomes, telemedicine offers provider benefits, according to Dr. Bretan. While the urologist has to travel quite a bit, for example, to do surgery once a week at a location 2 hours away, he says telemedicine allows him to manage and plan cases at a distance.

Telemedicine continues to face challenges in implementation and reimbursement. There are unanswered questions, according to Dr. Canon. “We don’t completely understand in which instances telemedicine is most beneficial and how all the parties involved, including physicians and nursing staff, and the patient and family, perceive it,” Dr. Canon said. “But I know this: In the U.S., we spend too much on health care, and we have to somehow lower the cost and maintain or improve the quality. In order to do that, we’re going to have to use technology.”

Telemedicine will move more into the forefront as medicine moves away from fee-for-service payment and toward managed care, capitated care, or bundled payments, Linkous said. “You don’t have to justify every time you see a patient using telemedicine. It’s part of the overall plan [of care],” Linkous said. “With all the revolution and evolution of health care that we’re going through, every bit of it favors increased payment for telemedicine.”

BIOMARKER

continued from page 1

the PSA result for the sensitivity that it gives us but then fine tune it with GPC-1, with the specificity demonstrated at 79% for prostate cancer patients.”

GPC-1 is a 558 amino acid-linked proteoglycan that occurs on the cell wall of prostate tissue. It functions as a co-receptor that regulates growth factor signaling.

In preclinical studies, a monoclonal antibody was developed—MIL-38—that binds GPC-1. Immunohistochemical staining showed no binding to normal prostate but did stain the majority of prostate cancers. A proof-of-concept study using urine samples showed a sensitivity of 71% and a specificity of 73% in discriminating between prostate cancer and normal tissues.

An ELISA kit (MiCheck) was developed, which detects GPC-1 in serum, plasma, and urine. Assay linearity was demonstrated over a working concentration of 10 pg/mL to 1.5 ng/mL. The calculated limit of detection was 3.4 pg/mL with a limit of quantitation at 7.2 pg/mL.

The purpose of the pilot study was to have a multicenter, retrospective non-randomized study to validate the future regulatory claims of the MiCheck technology. The objectives were to investigate the range of GPC-1 in normal tissue, benign tissue, and malignant tissue.

For this, the study included three arms with 115 subjects in each arm. Arm 1, the healthy arm with a normal digital rectal examination, included men older than 50 years with PSA <2.0 ng/mL (<3.0 ng/mL for men 60 years of age and older). Men with pathologically confirmed BPH or clinical BPH if PSA was in the normal range were enrolled in arm 2. Arm 3 constituted men with prostate cancer who were at least 1 week post-biopsy and had a Gleason score ≥7 to include only significant cancer.

“Further, we wanted to test the ability of the ELISA both alone and in combination with other biomarkers to improve the differentiation between non-cancers and cancerous prostate tissue compared with PSA alone,” said Dr. Henderson.

The study was led by Neal Shore, MD, medical director of Carolina Urologic Research Center, Myrtle Beach, SC, and was run by the CUSP research consortium across 10 tertiary community sites in the United States. The sponsor was Minomic International Ltd., of Sydney, Australia.

‘Very good correlation’ found

Very good correlation was found between both plasma and serum results for GPC-1, with circulating GPC-1 declining in prostate cancer, thereby significantly differentiating between normal and benign tissue compared with prostate cancer (p=0.035 for plasma and p=0.034 for serum).

Various GPC-1 cut points were assessed to maximize clinical utility (high specificity). Specificity was maximized at the cut points of 1.85 log in plasma and 1.95 log in serum to permit the test’s use as an adjunctive test to PSA to allow a better outcome for specificity. The specificity was 79% in plasma and 75% in serum for prostate cancer, with sensitivity of 32% and 37%, respectively. For prostate cancer patients with PSA of 4.0 to 10.0 ng/mL, specificity was 79% and sensitivity was 33%.

“GPC-1 shows significant promise in improving specificity, comparing prostate cancer to benign tissues,” Dr. Henderson said. “The likely clinical use of this molecule will be as an adjunctive test in patients who have an elevated PSA, specifically in that gray zone between 4.0 and 10.0 ng/mL.”

The next steps “are to engage the Early Detection Research Network, specifically validating those patients with PSA between 4.0 and 10.0 ng/mL, and then moving onto a pivotal trial of 1,200 patients, again using the CUSP consortium,” he said.

“The take-home message we found with this test is that the clinical utility is a high specificity.”

JONATHAN HENDERSON, MD

UT

“With all the revolution and evolution of health care that we’re going through, every bit of it favors increased payment for telemedicine.”

JONATHAN LINKOUS
American Telemedicine Association
Drug maker launches compounded formulations for IC, ED

San Diego—Imprimis Pharmaceuticals, Inc. has launched new compounded formulations for two urologic conditions—interstitial cystitis (IC) and erectile dysfunction (ED). Hep-Lido-A (alkalinized lidocaine and heparin) is a patented compounded formulation that is instilled directly into the bladder as an immediate treatment option for patients with IC. Hep-Lido-A’s new user-friendly kit includes a hydrophilic catheter and ready-to-use sterile pre-filled syringes (shown) compounded by an Imprimis pharmacy, providing convenience for in-office instillation and for patients who perform at-home instillations. Imprimis’ Tri-Mix (phentolamine, papaverine, and prostaglandin) lyophilized formulations are provided in a powder-like form in single-dose vials that can be transported and stored prior to reconstitution and self-administration for the treatment of ED. Tri-Mix formulations also allow for room-temperature storage.

For more information, visit www.imprimispharma.com.

Radiosurgery collimator allows treatment of broad range of tumors

Sunnyvale, CA—Accuray Inc. has introduced the InCise Multileaf Collimator (MLC) for the CyberKnife M6 radiosurgery system, which the company says is the first multileaf collimator to be available on a robotic platform. In evaluations completed by two U.S. sites, the main benefits of the MLC reported were the ability to treat a broader range of tumors than they could with fixed collimators or the Iris Collimator, and to do so with significantly increased efficiency. The CyberKnife M6 is designed to treat tumors anywhere in the body, including the prostate and kidney, according to Accuray.

For more information, visit www.accuray.com.

Laboratory now offers phi prostate cancer test to U.S. physicians

Rock Hill, SC—Physicians Choice Laboratory Services (PCLS) has added Beckman Coulter’s Prostate Health Index (phi) to the urologic health testing menu, providing access to physicians across the United States. The phi is a blood test that is three times more specific for the detection of prostate cancer than PSA alone, the only multi-analyte prostate cancer blood test with FDA approval, and the only multi-analyte blood test recommended in National Comprehensive Cancer Network Guidelines for prostate cancer early detection, according to PCLS. It helps physicians distinguish prostate cancer by combining three PSA markers (PSA, freePSA, and p2PSA) as part of an algorithm to accurately determine the probability of cancer in patients with elevated PSA levels and substantially reduce the number of negative biopsies.

For more information, visit www.pcls.com.

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Speak Out
What effect will SGR repeal have on your practice?

“I’m not familiar with the exact wording of the bill. I stopped paying attention last year. I used to write my congressman, but last year I decided it doesn’t make a difference. We’re just jumping through hoops like trained circus animals.

This new bill doesn’t change the way I feel because I know we can’t succeed in doing anything for ourselves. It’s part of their ultimate plan to do away with private practitioners. I’m part of a dying breed in the solo practice of urology. Doors are being closed by these large insurance companies and hospital corporations, so we see less and less patients.

This bill doesn’t make me feel better because I still feel the pressure to comply with the majority rule. They want everybody following guidelines and doing what everybody else is doing. We don’t want independence of thought. Big Brother is still watching.

I hope this bill really does change things, but I’ll believe it when I see it.”

W. Patrick Flanagan, Jr., MD
Waukesha, WI

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<th>Brand/Product</th>
<th>Page #</th>
<th>Website</th>
</tr>
</thead>
<tbody>
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<td>Vas Cutting Forceps</td>
<td>7</td>
<td><a href="http://www.accuratesurgical.com">www.accuratesurgical.com</a></td>
</tr>
<tr>
<td>Amgen</td>
<td>XGEVA</td>
<td>24-27</td>
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<td>XTANDI</td>
<td>45-CV4</td>
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<td>Healthcare Financial Institution</td>
<td>35</td>
<td><a href="http://www.carecredit.com">www.carecredit.com</a></td>
</tr>
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<td>CV2</td>
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<td>Clinical Innovation/Corporate</td>
<td>23</td>
<td><a href="http://www.cookmedical.com">www.cookmedical.com</a></td>
</tr>
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<td>Genentech</td>
<td>Immunotherapy-Bladder Clinical Trial</td>
<td>5</td>
<td><a href="http://www.gene.com">www.gene.com</a></td>
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<td>Decipher Prostate Cancer Classifier</td>
<td>33</td>
<td><a href="http://www.genomedx.com">www.genomedx.com</a></td>
</tr>
<tr>
<td>Genomic Health</td>
<td>Oncotype DX</td>
<td>21</td>
<td><a href="http://www.OncotypeDX.com/GPS">www.OncotypeDX.com/GPS</a></td>
</tr>
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<td>DefeatIC</td>
<td>13</td>
<td><a href="http://www.imprimispharma.com">www.imprimispharma.com</a></td>
</tr>
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<td>ZYTIGA</td>
<td>16 A-F*</td>
<td><a href="http://www.zytigahcp.com">www.zytigahcp.com</a></td>
</tr>
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<td>Flex-Xc</td>
<td>31</td>
<td><a href="http://www.karlstorz.com">www.karlstorz.com</a></td>
</tr>
<tr>
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<td>UroLift</td>
<td>37</td>
<td><a href="http://www.urolift.com">www.urolift.com</a></td>
</tr>
<tr>
<td>Northgate Technologies</td>
<td>Autolith Uro-Touch</td>
<td>29</td>
<td><a href="http://www.northgatetech.com">www.northgatetech.com</a></td>
</tr>
<tr>
<td>Physician Reimbursement Systems</td>
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<td><a href="http://www.prsnetwork.com">www.prsnetwork.com</a></td>
</tr>
</tbody>
</table>

I’m 66 years old, and I haven’t been satisfied with anything the federal government has done since they started Medicare. When I started practicing in ’82, reimbursement for a TURP was $1,250, which I thought was a huge amount of money. In 1983, the Medicare reimbursement was frozen, and in 1993 it dropped to $870. It’s still less than $900 today. With Blue Cross Blue Shield, a TURP can be reimbursed $2,400 for the surgical fee alone. My biggest issue with Medicare is that it’s the only entitlement program without a means test. I don’t trust politicians. They’ve never taken a cut in their pay.

I have serious questions as to how they’re going to put value-based pay on certain specialties. How do you assess the quality of a TURP? I’m glad we got away from the brink, but I’m not sure this will be any better or much different.

I’m not convinced it’s going to do anything major. I’m not convinced it will have a good handle on value-based reimbursements, and we’re going to see more and more health care provided by non-physicians. Good nurse practitioners and PAs refer sooner rather than later, but bad ones jump off on a workup that’s not focused and wind up with a lot of tests they don’t understand.”

Wm. Peter Horst, MD
Great Falls, MT

I’m employed by the university health system, so these things have very little direct effect on me. Changes to physician reimbursements don’t hugely affect us because the health system provides a huge buffer. If Medicare cuts reimbursements 5%, the health system still makes enough money; it doesn’t affect our pay.

Fee for service is not necessarily in the best interest of the patient. It’s more in the doctors’ interest. My dad was a urologist. Twenty or 30 years ago, he made 50% to 75% more than I make now, not accounting for inflation. So some doctors do marginally indicated things because they feel the need to make a certain living. I see this when patients want second opinions after seeing somebody in the community who wanted to do XYZ on them. You have a frank discussion and say, ‘You don’t need this.’ They tell you that’s not what they were told.

Basing reimbursement on quality, however, is hard to do on a practical level. Many things in the field of urology would be hard to measure; for example, surgical outcomes. Patients we see here may be very different from the patients seen in the community.”

William I. Jaffe, MD
Philadelphia
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New initiative would speed FDA approvals

Proposal also encourages telemedicine, repurposing of drugs

Washington—For urologists and other health care practitioners—and anybody who cares about having medicines to treat whatever disease might befall them—there is positive, bipartisan activity underway in Washington.

Despite the common perception of Congress being filled with a bunch of politically obsessed do-nothings, there actually is a determined and dedicated group of lawmakers and staff assistants who are working practically 24-7 to develop a sweeping new initiative that would help speed drug and device approvals and increase funding for new drug innovation.

Bill includes $10 billion for innovation fund

The so-called 21st Century Cures initiative, released in an updated 200-page document last week by bipartisan leaders of the House Energy and Commerce Committee, would steer $10 billion in mandatory spending into a National Institutes of Health (NIH) innovation fund over 5 years and authorize another $1.5 billion in discretionary dollars in each of the next 3 years. The innovation fund would be used for precision medicine, including funding the work of emerging young scientists.

The draft bill was released by Committee Chairman Fred Upton (R-MI); ranking minority member Frank Pallone, Jr. (D-NJ); Rep. Diana DeGette (D-CO); ranking minority member of the House Oversight and Investigations Subcommittee; Health Subcommittee Chairman Joe Pitts (R-PA); and ranking Health Subcommittee member Gene Green (D-TX). Upton said he would have a completed bill on the House floor for consideration this month (June).

The measure contains numerous provisions affecting the FDA, including reforming clinical trials and establishing an expedited approval pathway for certain medical devices, vaccines, and antibiotics.

A committee statement accompanying the discussion draft said it includes provisions to:

- foster development of treatments for patients facing serious or life-threatening diseases
- repurpose drugs for serious or life-threatening diseases and conditions
- modernize clinical trials
- help the development of personalized and precision medicines so the right patient can receive the right treatment at the right time
- provide for continued work in telehealth
- advance a truly interoperable health system

While work has been underway on the Cures initiative for more than a year, lawmakers have been unable to reach consensus on several key points, including how to encourage drug makers to take on the costly and time-consuming task of creating new drugs for rare diseases.

Initially, the plan was to grant longer exclusivity periods for manufacturers of seldom-used therapies for unmet medical needs, as well as giving U.S. generic drug manufacturers a longer protection time frame from foreign competitors. Both provisions have been dropped from the latest draft, as some advocacy groups raised concerns that a longer exclusivity period would increase costs to consumers while they waited for competitive versions to become available.

Other unresolved issues include areas related to telemedicine, the interoperability of health records, and repurposing FDA-approved drugs for other uses. However, there were reports that agreement may have been reached on some of these issues, including repurposing drugs.

During an Energy and Commerce Health Subcommittee hearing April 30, Pitts said an Energy and Commerce Committee Working Group on Telemedicine is working toward a “bipartisan proposal that will encourage the use of telemedicine services to improve health care quality and outcomes, increase patient access, and control costs.”

On repurposing drugs, Upton said at the hearing, “As we move through the process to markup, we will continue to work on a policy to provide incentives to develop drugs that, while they may have failed in trials for one indication, show promise to treat patients facing other serious or life-threatening diseases.”

Proposal raises concerns over safety

The legislation includes a streamlined process for the FDA to approve breakthrough therapies. It would allow the FDA to approve drugs with “early state clinical safety and effectiveness data,” giving manufacturers the responsibility of conducting post-approval studies. That provision worries watchdog and consumer groups.

“The bill emphasizes speed over safety,” said Vijay Das, health care policy advocate at Public Citizen.

There is agreement by many of the lawmakers involved in the development of the legislation that both the FDA and NIH need more money to handle their additional responsibilities, a difficult hurdle in today’s political environment.

“We are asking the FDA to make many changes to its current operation,” said Rep. DeGette, a lead sponsor of the bill with Upton. “We should make sure the agency has the resources to carry out these duties.”

Jeffrey Shuren, director of the FDA’s center for devices and radiological health, said the FDA’s purchasing power has declined over the past decade even as Congress expanded its responsibilities.

“We are excited that NIH gets more money,” said Shuren, “but all these great things don’t get out to the market unless we are in a position to help out. The more things that are piled up on people’s plates, the more they’re set up for failure.” UT

Fast Facts

The 21st Century Cures initiative:

- Is a bipartisan proposal that would steer $10 billion in mandatory spending into an NIH innovation fund over 5 years and authorize another $1.5 billion in discretionary dollars in each of the next 3 years
- Would reform clinical trials and establish an expedited approval pathway for certain medical devices, vaccines, and antibiotics
- Has raised concerns over safety due to a provision allowing the FDA to approve drugs with “early state clinical safety and effectiveness data”
Experimental agent shows promise against uropathogenic E. coli

AN INVESTIGATIONAL AGENT shows promise against uropathogenic Escherichia coli (UPEC), results of a recent study indicate.

For the study, which was published in PLOS Pathogens (2015; 11[4]), Victor Nizet, MD, and colleagues tested an experimental immune-boosting agent, AKB-4924, that stabilizes a protein called HIF-1alpha. This protein was shown to protect mice and human bladder cells from infection with UPEC.

“This new drug would be a treatment that would stimulate the body to produce its natural antimicrobials, which are many,” said Dr. Nizet, of the University of California, San Diego School of Medicine.

Dr. Nizet and colleagues found that using AKB-4924 in healthy human urinary tract cells made the cells more resistant to infection by UPEC.

OTC dietary supplement appears to treat, prevent prostate cancer

AN OVER-THE-COUNTER dietary supplement is effective in both treatment and prevention of prostate cancer in an animal model, according to a study online in the Journal of the National Cancer Institute (April 13, 2015).

The supplement, 4-methylumbelliferone (4-MU), is a non-toxic oral agent used in Europe and Asia to improve liver health.

Repeat sampling detects PCa in men with initial negative prostate Bx

AMONG A GROUP of men with negative prostate biopsy, cancer was still found in subsequent repeat sampling, according to a study published in the Journal of Urology (2015; 193:1178-84).

First author Nitya E. Abraham, MD, of New York University School of Medicine, and colleagues collected data on 1,837 men who underwent prostate biopsy. The authors found that 1,213 men had negative initial biopsies, and 798 repeat biopsies were performed in 255 men. They found that an increased likelihood of prostate cancer diagnosis was seen in men ≥70 years of age with repeat biopsies, biopsies including more than 20 cores, and the fourth repeat biopsy.

“What the continued likelihood of cancer detection even by the fifth biopsy, early consideration of saturation or image guided biopsy may be warranted in the repeat biopsy population,” the authors wrote.

WHAT'S GOOD FOR THE GUMS IS GOOD FOR THE PROSTATE

NEW RESEARCH suggests a link between the gums and the prostate, UPI reported.

Previous studies had shown a possible link between gum disease and prostatitis. Now, current research shows that treating gum disease improves prostatitis symptoms.

“This study shows that if we treat the gum disease, it can improve the symptoms of prostatitis and the quality of life for those who have the disease,” said lead author Nabil Bissada, PhD, of Case Western Reserve University, Cleveland.

In the study, which was published in Dentistry (2015; 5:285), the authors observed 27 male patients, 21 years of age and older, whose bloodwork showed elevated PSA levels.

The majority of the men were found to have little to no inflammation, but 15 had biopsy-confirmed malignancies. Two of the patients had both inflammation and a cancerous growth. All showed signs of gum disease. The authors found that after the men were treated for their gum disease—but not treated for their prostate symptoms—the majority experienced diminishing PSA levels. Most of those who had reported inflammation or trouble urinating experienced a lessening of their symptoms. Six men experienced no changes in symptoms or PSA levels.
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**INITIAL U.S. APPROVAL:** 2012

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

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

**INDICATIONS AND USAGE**

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

**CONTRAINDICATIONS**

Pregnancy: XTANDI can cause fetal harm when administered to a pregnant woman based on its mechanism of action. XTANDI is not indicated for use 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 (8.1)].

**WARRANTIES 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 patient with placebo experienced a seizure. Seizure occurred from 31 to 603 days after initiation of XTANDI. In Study 2, 1 of 671 (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 clinical 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 metastasis, 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.

**ADVERSE REACTIONS**

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

Two randomized clinical trials enrolled patients with metastatic prostate cancer that has progressed on androgen deprivation therapy (GnRH therapy or bilateral orchectomy), a disease setting that is also defined as metastatic CRPC. In both studies, patients received XTANDI 160 mg orally once daily in the active treatment arm or placebo in the control arm. All patients continued androgen deprivation therapy. Patients were allowed, but not required, to take glucocorticoids. The most common adverse reactions (≥ 10%) that occurred more commonly (≥ 2% over placebo) in the XTANDI-treated patients from the two randomized clinical trials were asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspepsia, musculoskeletal pain, weight decreased, headache, hypertension, and dizziness/vertigo.

Study 1: Metastatic Castration-Resistant Prostate Cancer Following Chemotherapy: Study 1 enrolled 1199 patients with metastatic CRPC who had previously received docetaxel. The median duration of treatment was 8.3 months with XTANDI and 3.0 months with placebo. During the trial, 48% of patients on the XTANDI arm and 46% of patients on the placebo arm received glucocorticoids.

Grade 3 and higher adverse reactions were reported among 47% of XTANDI-treated patients and 53% of placebo-treated patients. Discontinuations due to adverse events were reported for 16% of XTANDI-treated patients and 18% of placebo-treated patients. The most common adverse reaction leading to treatment discontinuation was seizure, which occurred in 0.9% of the XTANDI-treated patients compared to none (0%) of the placebo-treated patients. Table 1 shows adverse reactions reported in Study 1 that occurred at a ≥ 2% higher frequency in the XTANDI arm compared to the placebo arm.

**Table 1. Adverse Reactions in Study 1**

<table>
<thead>
<tr>
<th>Condition</th>
<th>XTANDI</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
<td>Grade 1-4 (%)</td>
</tr>
<tr>
<td>General Disorders</td>
<td></td>
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<tr>
<td>Asthenic Conditions</td>
<td>50.6</td>
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<td>Peripheral Edema</td>
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<td>Musculoskeletal And Connective Tissue Disorders</td>
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<td></td>
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<td>Back Pain</td>
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<td>Arthralgia</td>
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<td>Musculoskeletal Pain</td>
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<tr>
<td>Muscular Weakness</td>
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<td>Musculoskeletal Stiffness</td>
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<td>Gastrointestinal Disorders</td>
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<tr>
<td>Diarrhea</td>
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<tr>
<td>Vascular Disorders</td>
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<tr>
<td>Hot Flush</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Nervous System Disorders</td>
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<tr>
<td>Headache</td>
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<td>Dizziness</td>
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<tr>
<td>Psychiatric Disorders</td>
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<tr>
<td>Insomnia</td>
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<td>Anxiety</td>
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<td>Pollakiuria</td>
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<td>Fall</td>
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<td>Skin And Subcutaneous Tissue Disorders</td>
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<tr>
<td>Dry Skin</td>
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**Table 2. Adverse Reactions in Study 2**

<table>
<thead>
<tr>
<th>Condition</th>
<th>XTANDI</th>
<th>Placebo</th>
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<tbody>
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<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
<td>Grade 1-4 (%)</td>
</tr>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
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<tr>
<td>Asthenic Conditions</td>
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<td>Musculoskeletal And Connective Tissue Disorders</td>
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<td></td>
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<tr>
<td>Back Pain</td>
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<td>Hypertension</td>
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<tr>
<td>Nervous System Disorders</td>
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<td>Dizziness</td>
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<td>Dyspnea</td>
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<td>Lower Respiratory Tract And Lung Infection</td>
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<td>1.5</td>
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<tr>
<td>Psychiatric Disorders</td>
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<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>8.2</td>
<td>0.1</td>
</tr>
</tbody>
</table>
The composite AUC of enzalutamide of a strong CYP3A4 inhibitor (itraconazole) increased Pharmacology (12.3)].

Hypertension more severe in patients treated with XTANDI and included patients treated with placebo. Falls were not associated with enzalutamide compared to 4% of patients treated with placebo (0.5% Grade 3-4). In Study 2, 1 patient in each arm compared to 0.3% of patients treated with placebo (0.1% Grade 3-4) and 2% of patients treated with placebo (no Grade 3-4).

In the two randomized clinical trials, 11% of patients treated with XTANDI compared to 3% of patients treated with placebo died (0.1% Grade 3-4) and 2% of patients treated with placebo (no Grade 3-4).

Laboratory Abnormalities In the two randomized controlled 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 1-4 elevations in ALT occurred in 10% of patients treated with XTANDI (0.2% Grade 3-4) and 16% of patients treated with placebo (0.2% Grade 3-4). Grade 1-4 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).

Infection 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.

Falls and Fall-related Injuries In the two randomized clinical trials, falls including fall-related injuries, occurred in 9% of patients treated with XTANDI compared to 4% of patients treated with placebo. Falls were not associated with death or serious adverse reactions. Fall-related injuries were more severe in patients treated with XTANDI and included pathologic fractures, joint injuries, and hematomas.

Hypertension in the two randomized trials, hypertension was reported in 11% of patients receiving XTANDI and 4% of patients receiving placebo. No patients experienced a hypertensive crisis. Medical history of hypertension was balanced between arms. Hypertension led to study discontinuation in <1% of patients in each arm.

**Table 2. Adverse Reactions in Study 2 (cont.)**

<table>
<thead>
<tr>
<th>Renal And Urinary Disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematuria</td>
<td>8.8</td>
</tr>
<tr>
<td>Enuresis</td>
<td>1.3</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>5.8</td>
</tr>
<tr>
<td>Dysuria</td>
<td>1.3</td>
</tr>
</tbody>
</table>

**Injury, Poisoning And Procedural Complications**

Fall 12.7 1.6 5.3 0.7

**Non-Pathological Fracture**

Enzymatic Activity

Metabolism and Nutrition Disorders

Decreased Appetite 18.9 0.3 16.4 0.7

Investigations

Weight Decreased 12.4 0.8 8.5 0.2

Reproductive System and Breast Disorders

Gynecomastia 3.4 0.0 1.4 0.0

CYP2C8 induction potential is recommended. Moderate CYP2C8 inducers (e.g., bosentan, efavirenz, eraviren, modafinil, nafcillin) and St. John’s Wort may also reduce the plasma exposure of XTANDI and should be avoided if possible [see Clinical Pharmacology (12.3)].

**Effect of XTANDI on Drug Metabolizing Enzymes**

Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP3A49 inducer in humans. At steady state, XTANDI reduced the plasma exposure to midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate). Concomitant use of XTANDI with novel therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfenital, cyclosporine, diltiazem, ergotamine, fentanyl, imipramine, phenytoin, and trazodone) should be avoided, as enzalutamide may decrease their exposure. If co-administration with warfarin cannot be avoided, consider prothrombin INR monitoring [see Clinical Pharmacology (12.3)].

**USE IN SPECIFIC POPULATIONS**

**Pregnancy - Pregnancy Category X [see Contraindications (4)].**

**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 andXTANDI is not indicated for use in women, it is important to know that maternal use of XTANDI and receptor inhibitor could affect development of the fetus. Enzalutamide caused embryofetal toxicity in mice at exposures that were lower than in patients receiving the recommended dose. XTANDI is contraindicated in women who are or may become pregnant while 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 XTANDI.

**Animal Data**

In an embryo-fetal developmental toxicity study in mice, enzalutamide caused developmental toxicity when administered during organogenesis at ≥ 10 mg/kg/day, and cleft palate and anogenital distance at ≥ 10 mg/kg/day, and cleft palate and absent palate bone at 30 mg/kg/day. Doses of 30 mg/kg/day caused maternal toxicity. The doses tested into consideration the half-life of 5.8 days. In a dose escalation study, no seizures were reported at < 240 mg daily, whereas 3 seizures were reported, 1 each at 360 mg, 480 mg, and 600 mg daily. Patients may be at increased risk of seizure following an overdose.

**OVERDOSAGE**

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

**NONCLINICAL TOXICOLOGY**

Carcinogenesis, Mutagenesis, Impairment of Fertility

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, atrioventricular and septal vesicles were observed at ≥ 30 mg/kg/day (equal to the human exposure based on AUC). In 4-, 13- and 39-week studies in dogs, hypospermato genesis and atrophy of the prostate and epididymides were observed at ≥ 4 mg/kg/day (0.3 times the human exposure based on AUC).

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14B006-XTA-BRFS

Rx Only

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Important Safety Information

Contraindications XTANDI (enzalutamide) capsules can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. XTANDI is not indicated for use in women. XTANDI is contraindicated in women who are or may become pregnant.

Warnings and Precautions In Study 1, conducted in patients with metastatic castration-resistant prostate cancer (CRPC) who previously received docetaxel, seizure occurred in 0.9% of patients who were treated with XTANDI and 0% treated with placebo. In Study 2, conducted in patients with chemotherapy-naïve metastatic CRPC, seizure occurred in 0.1% of patients who were treated with XTANDI and 0.1% treated with placebo. Patients experiencing a seizure were permanently discontinued from therapy and all seizure events resolved. There is no clinical trial experience re-administering XTANDI to patients who experienced a seizure, and limited clinical trial experience in patients with predisposing factors for seizure. Study 1 excluded the use of concomitant medications that may lower 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 during which sudden loss of consciousness could cause serious harm to themselves or others. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

Adverse Reactions The most common adverse reactions (≥10%) reported from the two combined clinical trials that occurred more commonly (≥2% over placebo) in the XTANDI-treated 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.

Other Adverse Reactions include:
• Laboratory Abnormalities: In the two studies, 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 on placebo (0.5% Grade 3-4). Grade 1-4 elevations in ALT occurred in 10% of patients treated with XTANDI (0.2% Grade 3-4) and 16% of patients treated with placebo (0.2% Grade 3-4).

Grade 1-4 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 XTANDI versus 0.3% of placebo patients and in Study 2, 1 patient in each treatment group (0.1%) had an infection resulting in death.
• Falls: In the two studies, falls including fall-related injuries occurred in 9% of XTANDI patients vs. 4% treated with placebo. Falls were not associated with loss of consciousness or seizure. Fall-related injuries were more severe in XTANDI patients and included non-pathologic fractures, joint injuries, and hematomas.
• Hypertension: In the two studies, hypertension was reported in 11% of patients receiving XTANDI and 4% of patients receiving placebo. No patients experienced hypertensive crisis. Medical history of hypertension was balanced between arms. Hypertension led to study discontinuation in <1% of XTANDI or placebo treated patients.

Drug Interactions
• Effect of Other Drugs on XTANDI - Administration of strong CYP2C8 inhibitors can increase the plasma exposure to XTANDI. Co-administration of XTANDI with strong CYP2C8 inhibitors should be avoided if possible. If co-administration of XTANDI cannot be avoided, reduce the dose of XTANDI. Co-administration of XTANDI with strong or moderate CYP3A4 and CYP2C8 inducers may alter the plasma exposure of XTANDI and should be avoided if possible.
• Effect of XTANDI on Other Drugs - XTANDI is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. 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.

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94% of insured patient lives are covered for XTANDI*2
*As of February 2015. A product’s placement on a plan formulary involves a variety of factors known only to the plan and is subject to eligibility.

To learn more, please visit XtandiHCP.com
Select Safety Information

XTANDI can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. XTANDI is not indicated for use in women. XTANDI is contraindicated in women who are or may become pregnant.

Seizure occurred in 0.9% of patients receiving XTANDI who previously received docetaxel and in 0.1% of patients who were chemotherapy-naive. 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.


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