Painful truth

In U.S. opioids crisis, urologists are part of the problem—and solution

Lisette Hilton / UT Correspondent

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That’s a big practice shift for Dr. Davies, who not long ago would prescribe 20, 30, or more oxycodone or other narcotic pills to urologic surgery patients. It was the norm, he said.

“We didn’t have any particular data per procedure on how much to give. We kind of eyeballed it. Bigger procedures got bigger prescriptions,” said Dr. Davies, associate professor of urology at the University of Pittsburgh School Of Medicine. “We just wanted to make sure our patients didn’t have pain.”

Strong evidence has emerged in recent years suggesting opioid prescribers, including well-meaning urologists, have helped to fuel a national crisis and opioid addiction epidemic. Every day, more than 115 people in this country die because they’ve overdosed on opioids, including prescription pain relievers, according to the National Institute on Drug Abuse.

“The current opioid crisis is the third opioid epidemic in the history of the U.S., according to urologist Francis J. McGovern, MD, assistant clinical professor of surgery at Harvard Medical School, Massachusetts General Hospital, Boston.

“This most recent opioid epidemic began in the late 1990s and parallels the initiation of pain as the fifth vital sign, which is the result of unfortunate misguided bureaucracies."

Please see OPIOIDS, on page 45

OPIOIDS IN UROLOGIC PRACTICE

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Researchers achieved a 46% reduction in opioid use among patients who underwent a range of urologic cancer surgeries without increasing their pain or anxiety.4


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Please see a brief summary of prescribing information for GLYDO (lidocaine HCl jelly USP, 2%) on the next page.


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GLYDO (lidocaine HCl jelly USP, 2%)  
Brief Summary of Prescribing Information

INDICATIONS AND USAGE  
GLYDO (lidocaine HCl jelly USP, 2%) is indicated for prevention and control of pain in procedures involving the mouth and male and female urethra, for topical treatment of painful urerithrus, and as an anesthetic lubricant for endotracheal intubation (oral and nasal).

CONTRAINDICATIONS  
Lidocaine is contraindicated in patients with a known history of hypersensitivity to local anesthetics of the amide type or to other components of GLYDO.

WARNINGS  
EXCESSIVE DOSAGE, OR SHORT INTERVALS BETWEEN DOSES, CAN RESULT IN HIGH PLASMA LEVELS AND SERIOUS ADVERSE EFFECTS. PATIENTS SHOULD BE INSTRUCTED TO DECIDE BEFORE THE ADMINISTRATION OF THE PRESCRIBED DOSAGE AND ADMINISTRATION GUIDELINES AS SET FORTH IN THIS PACKAGE INSERT.  
THE MANAGEMENT OF SERIOUS ADVERSE REACTIONS MAY REQUIRE THE USE OF RESUSCITATIVE EQUIPMENT, OXYGEN, AND OTHER RESUSCITATIVE DRUGS.

GLYDO should be used with extreme caution in the presence of sepsis or severely traumatized mucosa in the area of application, since under such conditions there is the potential for rapid systemic absorption. When used for endotracheal tube lubrication care should be taken to avoid introducing the product into the lumen of the tube. Do not use the jelly lubricant on endotracheal intubations. If allowed into the inner lumen, the jelly dry on the inner surface leaving a residue which tends to clump with flexion, narrowing the lumen. There have been rare reports in which this residue has caused the lumen to occlude. (See also ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION.)

PRECAUTIONS  
General  
The safety and effectiveness of lidocaine depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. (See WARNINGS and ADVERSE REACTIONS.) The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. Repeated doses of lidocaine may cause significant increases in blood levels with each repeated dose because of slow accumulation of the drug or its metabolites. Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly patients, acutely ill patients, and children should be given reduced doses commensurate with their age and physical status. Lidocaine should also be used with caution in patients with severe shock or heart block.

GLYDO should be used with caution in patients with known drug sensitivities. Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. Since it is not known whether amide-type local anesthetics may trigger this reaction and since the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard protocol for management of crises should be available. Signs of malignant hyperthermia (tachycardia, tachypnea, labile blood pressure, and metabolic acidosis) may precede temperature elevation. Successful outcome is dependent on early diagnosis, prompt discontinuance of the suspect triggering agent(s) and institution of treatment, including oxygen therapy, indicated supportive measures and dantrolene (consult dantrolene sodium intravenous package insert before using).

Information for Patients  
When topical anesthetics are used in the mouth, the patient should be aware that the production of topical anesthesia may impair swallowing and thus enhance the danger of aspiration. For this reason, food should not be ingested for 60 minutes following use of local anesthetic preparations in the mouth or throat area. This is particularly important in children because of their frequent oral intake.

Number of the tongue or buccal mucosa may enhance the danger of unintentional biting trauma. Food and chewing gum should not be taken while the mouth or throat area is anesthetized.

Carcinogenesis—Long-term studies in animals have not been performed to evaluate the carcinogenic potential of lidocaine.

Mutagenesis—The mutagenic potential of lidocaine has been tested in the Ames Salmonella reverse mutation assay, in an vitro chromosome aberration assay in human lymphocytes and in an in vivo mouse micronucleus assay. There was no indication of any mutagenic effects in these studies.

Impairment of Fertility: The effects of lidocaine on fertility was examined in the rat model. Administration of 30 mg/kg, i.e., (700 mg/m²) to the mating pair did not produce alterations in fertility or general reproductive performance of rats. There are no studies that examine the effect of lidocaine on sperm parameters. There was no evidence of altered fertility.

Use in Pregnancy  
Teratogenic Effects: Pregnancy Category B  
Reproductive studies for lidocaine have been performed in both rats and rabbits. There was no evidence of harm to the fetus at subcutaneous doses of up to 50 mg/kg lidocaine (300 mg/m² on a body surface area basis) in the rat model. In the rabbit model, there was no evidence of harm to the fetus at a dose of 5 mg/kg, s.c. (60 mg/m² on a body surface area basis). Treatment of rabbits with 25 mg/kg (300 mg/m²) produced evidence of maternal toxicity and evidence of delayed fetal development, including a non-significant increase in fetal weight (7%) and an increase in minor skeletal anomalies (skull and sternal defect, reduced ossification of the phalanges). The effect of lidocaine on postnatal development was examined in rats by treating pregnant female rats daily subcutaneously at doses of 2, 10, and 50 mg/kg (30, 150, and 300 mg/m²) from day 15 of pregnancy and up to 20 days post-partum. No signs of adverse effects were seen either in dams or in the pups up to and including the dose of 10 mg/kg (60 mg/m²); however, the number of surviving pups was reduced at 50 mg/kg (300 mg/m²), both at birth and the duration of lactation period, the effect most likely being secondary to maternal toxicity. No other effects on litter size, litter weight, abnormalities in the pups and physical developments of the pups were seen in this study. A second study examined the effects of lidocaine on postnatal development in the rat that included assessment of the pups from weaning to sexual maturity. Rats were treated for 8 months with 10 or 30 mg/kg, s.c. lidocaine (60 mg/m² and 180 mg/m² on a body surface area basis, respectively). This time period encompassed 3 mating periods. There was no evidence of altered postnatal development in any offspring; however, both doses of lidocaine significantly reduced the average number of pups per litter surviving until weaning of offspring from the first 2 mating periods.

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

Labor and Delivery  
Lidocaine is not contraindicated in labor and delivery. Should GLYDO be used concomitantly with other products containing lidocaine, the total dose contributed by all formulations must be kept in mind.

Nursing Mothers  
Lidocaine is secreted in human milk. The clinical significance of this observation is unknown. Caution should be exercised when lidocaine is administered to a nursing woman.

Pediatric Use  
Although, the safety and effectiveness of GLYDO in pediatric patients have not been established, a study of 19 premature neonates (gestational age <33 weeks) found no correlation between the plasma concentration of lidocaine or monoethylglycinexylidide and infant body weight when moderate amounts of lidocaine (i.e. 0.3 mg/kg of lidocaine gel 20 mg/mL) were used for lubricating both intranasal and endotracheal tubes. No neonates had plasma levels of lidocaine above 750 mg/L. Dosages in children should be reduced, commensurate with age, body weight, and physical condition. (See DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS  
Adverse experiences following the administration of lidocaine are similar in nature to those observed with other amide local anesthetic agents. These adverse experiences are, in general, dose-related and may result from high plasma levels caused by excessive dosage or rapid absorption, or may result from a hypersensitivity, idiosyncrasy, or diminished tolerance on the part of the patient. Serious adverse experiences are generally systemic in nature. The following types are those most commonly reported.

There have been rare reports of endotracheal tube occlusion associated with the presence of dried jelly residue in the inner lumen of the tube. (See also WARNINGS and DOSAGE AND ADMINISTRATION.)

Central Nervous System  
CNs manifestations are excitation and/or depression and may be characterized by light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tremors, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression, and arrest. The excitation manifestations may be very brief or may not occur at all, in which case the first manifestation of toxicity may be drowsiness merging into unconsciousness and respiratory arrest. Drowsiness following the administration of lidocaine is usually an early sign of a high blood level of the drug and may occur as a consequence of rapid absorption.

Cardiovascular System  
Cardiovascular manifestations are usually depressant and are characterized by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest.

Allergic  
Allergic reactions are characterized by cutaneous lesions, urticaria, edema, or anaphylactoid reactions. Allergic reactions may occur as a result of sensitivity either to the local anesthetic agent or to other components in the formulation. Allergic reactions as a result of sensitivity to lidocaine are extremely rare and, if they occur, should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

OVERDOSAGE  
Acute emegencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use of local anesthetics. (See ADVERSE REACTIONS, WARNINGS, and PRECAUTIONS.)

Management of Local Anesthetic Emergencies  
The first consideration is prevention, best accomplished by careful and constant monitoring of cardiovascular and respiratory vital signs and the patient’s state of consciousness after each local anesthetic administration. At the first sign of change, oxygen should be administered.

The first step in the management of convulsions consists of immediate attention to the maintenance of a patent airway and assisted or controlled ventilation with oxygen and a delivery system capable of permitting immediate positive airway pressure by mask. Immediately after the institution of these ventilatory measures, the adequacy of the airway should be evaluated, keeping in mind that drugs used to treat convulsions sometimes depress the circulation when administered intravenously. Should convulsions persist despite adequate respiratory support, and if the status of the circulation permits, small increments of a ultra-short acting barbiturate (such as thiopental or thiamylal) or a benzodiazepine (such as diazepam) may be administered intravenously. The clinician should be familiar, prior to the administration of local anesthetics, with these anticonvulsant drugs. Supportive treatment of circulatory depression may require administration of intravenous fluids and, when appropriate, a vasopressor as directed by the clinical situation (e.g., ephedrine).

If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias, and cardiac arrest. If cardiac arrest should occur, standard cardiolypulmonary resuscitative measures should be instituted.

Diagnosis is of negligible value in the treatment of acute overdose with lidocaine.

The oral LD₅₀ of lidocaine HCl in non-fasted female rats is 459 (346 to 773) mg/kg (as the salt) and 214 (159 to 324) mg/kg (as the salt) in fasted female rats.

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Novel method in the diagnostic arsenal for prostate cancer

SIGRID CARLSSON, MD, PhD, MPH
Dr. Carlsson is assistant attending epidemiologist, departments of urology (service) and epidemiology and biostatistics, Memorial Sloan Kettering Cancer Center, New York, and department of urology, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden.

Screening for prostate cancer by measuring the concentration of PSA in blood is a contentious issue, as the specificity of the PSA test is modest. The scientific community is working to develop novel methods to distinguish aggressive from indolent prostate cancer. The 2018 National Comprehensive Cancer Network Prostate Cancer Early Detection guideline suggests considering free/total PSA, pbi, 4k, score, and PCA—tests that have been evaluated in dozens of scientific papers and thousands of patients, including prospective multicenter evaluations. When any of these methods are used as a “reflex” test in men with an indication for biopsy, they have shown improved accuracy over the PSA test and have significantly reduced the need for biopsy.

Multiparametric magnetic resonance imaging (MRI) is gaining traction as a diagnostic tool in the pre-biopsy setting and has been shown in several large-scale randomized controlled trials to improve the cancer detection rate when combined with transrectal ultrasound fusion biopsies compared to systematic biopsy alone.

I commend Dr. Klein and colleagues for evaluating a new diagnostic tool that could enhance the field of prostate cancer detection: the IsoPSA assay (see page 5). This test utilizes an intriguing laboratory technique that measures the protein structure of free and complex PSA, which is then mathematically converted to a predicted risk of high-grade cancer. In the initial prospective study of 261 men with biopsies and total PSA levels ≥2.0 ng/mL, IsoPSA outperformed total PSA in predicting high-grade prostate cancer (area under the curve [AUC]: 0.81 [95% CI: 0.74–0.86]) and had a favorable “net benefit” (ie, balancing caught vs. missed cancers as well as risks with biopsy) compared to performing biopsies based on a risk calculator (Eur Urol 2017; 72:942–9).

A small prospective validation study of 123 biopsied men with total PSA levels ≥2.0 ng/ mL, of whom many had an MRI-guided biopsy in addition to systematic biopsy, confirmed an AUC of 0.82, with a reduction in unnecessary biopsies by 47% and missed/delayed detection of 2% of high-grade cancers (J Urol 2018;199 [suppl]:e1147–9).

While these initial studies are interesting, there is a critically important need for additional large-scale, prospective and comparative studies before we can determine the clinical utility of IsoPSA. For instance, how does the test perform as compared to free/total PSA or other biomarkers based on isoform concentrations, with/without the use of MRI and with/without clinical information in the mathematical model? Answers to this and other questions will decide whether IsoPSA could be a notable addition in our diagnostic arsenal to distinguish aggressive from indolent prostate cancer.

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To read more about PCa diagnostics, see Assay predicts high-grade PCa on page 5

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ASSAY predicts high-grade PCa

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Over-detection of low-grade cancer as a reflex test is likely to reduce over-detection of low-grade Ca

San Francisco—Results of a prospective, multicenter study validate the clinical performance of a PSA isoform assay (IsoPSA) for predicting high-grade prostate cancer, Eric A. Klein, MD, reported at the AUA annual meeting in San Francisco.

“Current assays that measure PSA are prostate specific but not cancer specific, and therefore, they lead to a lot of unnecessary biopsies,” said Dr. Klein. Andrew C. Novick Distinguished Chair, Glickman Urological and Kidney Institute, and professor of surgery, Lerner College of Medicine of Cleveland Clinic, Cleveland.

“We believe that [use of IsoPSA] as a reflex test is likely to reduce over-detection of low-grade cancer and also the rate of unnecessary biopsies by an estimated 47%.”

Eric A. Klein, MD

The IsoPSA assay is a novel biomarker that predicts cancer risk based on measuring the structure rather than the concentration of prostate cancer-specific isoforms. We believe that its use as a reflex test is likely to reduce over-detection of low-grade cancer and also the rate of unnecessary biopsies by an estimated 47%.

Using a small sample of blood placed into a proprietary aqueous solution, IsoPSA measures PSA isoforms that arise because the disordered metabolism of cancer cells results in molecular truncation and glycosylation, causing changes in physical structure.

Its performance for predicting Gleason grade ≥7 disease was demonstrated in an initial study that included 261 men with PSA ≥2 ng/mL who were undergoing prostate biopsy within 30 days. The prevalence of high-grade disease in the study population was 33.7%, and the PSA isoform test had an area under the curve (AUC) of 0.81 for predicting Gleason grade ≥7, 96% sensitivity, and a negative predictive value (NPV) of 95%. The AUC for total PSA was 0.68, and there was no relationship between the IsoPSA value and serum PSA.

“A lot of men in the study cohort who had a very low PSA would be considered at high risk for having high-grade disease based on their IsoPSA result,” Dr. Klein said.

The validation study included 271 men with a PSA ≥2 ng/mL who had blood obtained within 30 days prior to prostate biopsy; the prevalence of high-grade disease in this cohort was 29.5%. The performance of IsoPSA in the validation study was statistically similar to the preliminary analysis. The AUC for predicting Gleason grade ≥7 disease was 0.7%, and the test’s sensitivity and NPV were both 93%. The AUC for total PSA was 0.66.

Assay performs better in men undergoing MRI-guided Bx

Dr. Klein pointed out that the percentage of men undergoing magnetic resonance imaging-ultrasound fusion biopsy was higher in the validation study than in the initial study (42% vs. 4%). A subgroup analysis in the validation cohort with men categorized by biopsy type (MRI-guided or transrectal ultrasound) showed the assay performed better in men undergoing an MRI-guided assay than those having a transrectal ultrasound-guided biopsy both for predicting the presence of any cancer (AUC 0.82 vs. 0.78) and Gleason grade ≥7 disease (AUC 0.86 vs 0.83).

“One would expect that a test that predicts the presence of high-grade disease should perform better when it is used in men who undergo biopsy with a technique that is more likely to find high-grade disease, and in fact, it did,” said Dr. Klein.

Results of a multivariable analysis found that the IsoPSA result was the only variable that independently predicted Gleason grade ≥7 disease in both the initial and validation studies. Age was a significant variable in the initial study only, and there were no significant associations between presence of high-grade disease and total PSA, prostate volume, or race in either study.

“This finding suggests that IsoPSA will be a very simple test to use,” Dr. Klein said.

Based on the findings from the initial and validation studies, Dr. Klein proposed a screening algorithm in which IsoPSA would be ordered as the next step for all men with a worrisome total serum PSA. Men with a negative IsoPSA would be monitored while those with a positive test result would be considered candidates for MRI-ultrasound fusion biopsy.

“The role of MRI-ultrasound fusion biopsy for prostate cancer detection in the setting of PSA screening is controversial, in part because it misses about 20% of high-grade disease. I would argue that a biopsy is justified in a patient who tests positive with an assay that has high sensitivity for detecting the presence of Gleason grade 7 or higher prostate cancer, even if the MRI is negative,” he said.

Cleveland Clinic has a financial interest in Cleveland Diagnostics, which owns the intellectual property for IsoPSA with AnalizaDx. Genomic Health has licensed this intellectual property for commercial development.

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STUDY: WATER INTAKE PREVEN TS RECURRENT CYSTITIS
Premenopausal women with recurrent cystitis who drank more water had less frequent infections in a randomized clinical trial.

The study, which was published online in JAMA Internal Medicine (Oct. 1, 2018), included 140 women with recurrent cystitis who reported drinking less than 1.5 liters of total fluid daily. During the 12 months of the trial, half the women were assigned to drink 1.5 liters of water in addition to their regular fluids, while the other women did not change their regular fluid intake.

Episodes of cystitis were less frequent in women who drank more water for 12 months; the average number of cystitis episodes was 1.7 for the women who drank more water compared with 3.2 for the women who didn’t.

“Increased water intake is an effective antimicrobial-sparing strategy to prevent recurrent cystitis in premenopausal women at high risk for recurrence who drink low volumes of fluid daily,” concluded the authors, led by Thomas M. Hooton, MD, of the University of Miami Miller School of Medicine.
IMRT ownership appears to influence PCa treatment

Retrospective study identifies wide variation in treatment rates, spending

Benjamin P. Saylor
Content Managing Editor

SAN FRANCISCO—Physician ownership of intensity-modulated radiation therapy (IMRT) facilities appears to influence the way men with newly diagnosed prostate cancer are treated, according to a recent study presented at the AUA annual meeting in San Francisco.

Previous studies have found an association between IMRT ownership and increased use of radiation therapy, Tudor Borza, MD, MS, explained. However, these studies have been criticized for their choice of control groups, lack of generalizability, and the fact that they did not evaluate IMRT ownership’s effect on overall treatment of prostate cancer, said Dr. Borza, who was a urologic oncology and health services research fellow at the University of Michigan, Ann Arbor, at the time of the study, working with Brent K. Hollenbeck, MD, MS, and colleagues. He is currently assistant professor of urology at the University of Wisconsin School of Medicine and Public Health, Madison.

For the current study, Dr. Borza presented data from a retrospective cohort of 19,063 men from a 20% Medicare sample. The authors sought to evaluate the effect of IMRT ownership on initial prostate cancer treatment (defined as receipt of radiation therapy, surgery, or cryotherapy within 1 year of diagnosis), treatment in men least likely to benefit (defined as treatment in patients with 10-year risk of non-cancer mortality >75%), and annual per-beneficiary price standardized spending.

The men were age 66 years or older and were diagnosed with prostate cancer between 2010 and 2013, with 1-year follow-up through the end of 2014.

The men in the study were cared for by urologists representing 561 single-specialty groups. The authors performed Internet searches to determine IMRT ownership, looking for practices whose websites advertise IMRT services or who employed at least one radiation oncologist. They identified 88 practices.

Wide variation in initial treatment

The authors found wide variation in initial treatment, with treatment rates ranging from 47% to 87% and most of the IMRT-owning groups clustered “well above” the mean rate of 70%, according to Dr. Borza. Sixteen percent of IMRT-owning groups were below the mean, while 57% were in the highest quartile.

For treatment in men least likely to benefit, the variation was greater, ranging from 15% to 80%. Fourteen percent of IMRT-owning groups were below the mean rate of treatment of 44%, while 43% were in the highest quartile.

Annual spending ranged from $12,865 to $34,964, with a mean of $20,668. Eleven percent of IMRT-owning groups had spending below the mean, while 68% were in the highest quartile.

“These data are suggestive of the fact that IMRT ownership clearly plays a role in the way men with newly diagnosed prostate cancer are treated,” Dr. Borza said.

Early-life alcohol intake raises PCa risk

Cumulative lifetime intake also associated with high-grade prostate cancer, data indicate

Lisette Hilton
UT Correspondent

Researchers studying alcohol consumption in men having prostate biopsies found those reporting heavy drinking earlier in life were more likely to have high-grade prostate cancer, whereas men’s current alcohol intake didn’t appear to impact the severity of their diagnoses.

“The World Cancer Research Fund recently issued a recommendation to avoid alcohol for the purposes of cancer prevention. This recommendation is based on the established role of alcohol in risk of oral and gastrointestinal cancers, and additional research is required to understand if alcohol plays a role in prostate cancer,” said senior author Emma H. Allott, PhD, who conducted the research when she was an assistant professor of nutrition at the

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ALCOHOL
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University of North Carolina Chapel Hill’s Gillings School of Global Public Health.

Currently, Dr. Allott is a lecturer in molecular cancer epidemiology at Queen’s University Belfast, Northern Ireland.

Despite increasing evidence that alcohol is a risk factor for many other cancer types, alcohol’s effect on prostate cancer is unclear. Studies looking at men’s current drinking and prostate cancer risk have yielded conflicting results. Researchers examining lifetime alcohol exposure and prostate cancer risk seem to show a positive association with low- and high-grade prostate cancer. Some of those studies have suggested an association between early-life alcohol consumption and prostate cancer, but few researchers have looked specifically at how drinking early in life might impact prostate cancer or cancer grade later.

“Potentially, research studies assessing alcohol intake around the time of prostate cancer diagnosis may miss any effect of alcohol on prostate cancer,” Dr. Allott said.

“Currently, little is known about how alcohol may influence prostate cancer risk and progression. As such, it may be too soon for urologists to counsel their patients about alcohol with respect to prostate cancer.”

EMMA H. ALLOTT, PhD

The evidence suggests that prostate carcinogenesis might span decades, which makes considering early-life alcohol exposure important for better understanding prostate cancer etiology, the authors wrote. The study was published in Cancer Prevention Research (Aug. 23, 2018 [Epub ahead of print]).

Dr. Allott and co-authors studied data from a racially diverse cohort of 650 men undergoing a prostate biopsy at the Durham Veterans Affairs Medical Center between January 2007 and January 2018. Men in the study completed a questionnaire about how much alcohol they consumed, from none to seven or more drinks weekly, during each decade of their lives.

They found that men who drank seven or more drinks weekly at ages 15 to 19 years were 3.2 times more likely to be diagnosed with high-grade prostate cancer later in life compared to non-drinkers.

“The authors noted similar associations between heavier drinking and prostate cancer severity for ages 20 to 29, 30 to 39, and 40 to 49 years. Men with a cumulative lifetime intake of seven or more alcoholic beverages weekly also were 3.2 times more likely than lifetime non-drinkers to have high-grade prostate cancer later in life. The authors concluded that their results suggest earlier-life and cumulative alcohol consumption might be important considerations when analyzing prostate cancer risk. But it’s premature to make any recommendations based on the results of this study alone. Further research is needed, according to Dr. Allott.

No link between intake, overall PCa Dx at biopsy
There was no association, however, between alcohol intake at ages 15 to 19 years and overall prostate cancer diagnosis at biopsy. And current alcohol consumption was not significantly associated with high-grade prostate cancer.

Among the study’s limitations, it relied on self-reported data, which is subject to bias. UTL
Checkpoint inhibitor found efficacious in elderly patients

Cheryl Guttman Krader
UT Contributing Editor

Retrospective analyses of data collected in a real-world study provide assurance about using nivolumab (Opdivo) to treat elderly patients with metastatic renal cell carcinoma (mRCC) who have failed previous therapy.

The recently published research (PLoS One 2018; 13:e0199642) was conducted recognizing that while approximately one-half of patients newly diagnosed with RCC are ≥65 years of age, there is a paucity of information about the activity of nivolumab in older patients. To provide insight about the efficacy and safety of nivolumab in older patients, the study analyzed data from the Italian cohort of the nivolumab Expanded Access Program (EAP) that provided the immune checkpoint inhibitor to patients with mRCC whose disease had progressed despite treatment with other therapies considered standard of care.

Of 389 patients enrolled in the EAP across 95 centers in Italy, 125 (32%) were elderly (age ≥70 years) and 70 patients (18%) were considered “very elderly” (age ≥75 years). The results of the analyses showed that the efficacy of nivolumab in the elderly subgroup of the Italian EAP cohort was similar to that observed in the overall EAP population and in the pivotal, phase III CheckMate-025 trial, which compared nivolumab to everolimus (Afinitor) as treatment for mRCC following prior antiangiogenic-based therapy.

“Safety was comparable between the elderly patients and the overall EAP population, and was consistent with what previously reported,” wrote the authors, led by Maria Giuseppa Vitale, MD, of Azienda Ospedaliera Universitaria di Modena, Modena, Italy.

Adverse events in elderly patients treated with nivolumab in the EAP cohort were also comparable to those seen in the overall EAP population and to those previously reported.

Alexander Kutikov, MD, chief of urology and urologic oncology and professor of surgical oncology at Fox Chase Cancer Center, Philadelphia, noted, “Nivolumab in combination with ipilimumab (Yervoy) is currently one of the first-line treatments for stage IV kidney cancer. Yet, over the years, many patients received and are now progressing through VEGF targeted therapy. For these patients, second-line nivolumab monotherapy is an option.”

TABLE NIVOLUMAB FOR mRCC: EFFICACY, SAFETY BY AGE GROUP

<table>
<thead>
<tr>
<th>Objective response rate</th>
<th>Overall cohort</th>
<th>Elderly patients (age ≥70 years)</th>
<th>Very elderly patients (age ≥75 years)</th>
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<tbody>
<tr>
<td></td>
<td>23%</td>
<td>27%</td>
<td>28%</td>
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<tr>
<td>Rate of stable disease</td>
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<td></td>
<td>32%</td>
<td>35%</td>
<td>34%</td>
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<tr>
<td>12-month overall survival rate</td>
<td>64.1%</td>
<td>77.8%</td>
<td>77.7%</td>
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<tr>
<td>Treatment-related adverse event incidence</td>
<td>33%</td>
<td>37%</td>
<td>40%</td>
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<tr>
<td>Fatigue</td>
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<td></td>
<td>13%</td>
<td>17%</td>
<td>19%</td>
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<tr>
<td>Rate of Grade 3 or 4 treatment-related adverse events</td>
<td>7%</td>
<td>5%</td>
<td>4%</td>
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<tr>
<td>Rate of Grade 3 or 4 fatigue</td>
<td></td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Rate of discontinuation due to treatment-related adverse event</td>
<td>8%</td>
<td>8%</td>
<td>12%</td>
</tr>
</tbody>
</table>

Source: Maria Giuseppa Vitale, MD

“This report again underscores that in appropriately selected groups, age by itself fails to be a predictor of adverse events or treatment failure.”

ALEXANDER KUTIKOV, MD

“The study published in PLoS One reports safety and efficacy data on nivolumab as monotherapy without ipilimumab in patients who received and progressed through previous targeted therapy. Although a large portion were older than age 70, the vast majority had excellent performance status. This report again underscores that in appropriately selected groups, age by itself fails to be a predictor of adverse events or treatment failure. This is important since ≥50% of patients who are diagnosed with RCC are over 65 years of age at presentation,” said Dr. Kutikov, who was not involved with the study.

Patients were eligible for enrollment in the EAP if they were ≥18 years of age, had histologically confirmed advanced or metastatic RCC with a clear-cell component, and had received at least one prior therapy for their advanced/metastatic disease. They received nivolumab, 3 mg/kg by intravenous infusion every 2 weeks for up to 24 months, or until unacceptable toxicity, clear disease progression, or withdrawal of informed consent, although the protocol included defined circumstances allowing for continued treatment despite progression.

Within the subgroup of elderly patients, the median age was 75 years, 75% were male, 92% had an ECOG performance status of 0 or 1, and lung was the most common site of metastasis (73%).

During a median follow-up of 11.9 months, the objective response rate was 23% for the overall EAP cohort and 27% and 28% in the elderly and very elderly subgroups, respectively. The rates of stable disease in the overall, elderly, and very elderly groups were 32%, 35%, and 34%, respectively.

OS higher in older cohorts
Overall survival rates were also numerically higher in the older cohorts compared with the overall population; for the entire cohort and the ≥70 years

Please see RCC AGENT, on page 10
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† Data on file (2013 internal study), Teleflex Incorporated, Report #D001591. Testing conducted on porcine carotids, sample size = 33, p = 0.05. Clinical performance cannot be extrapolated from the data. Testing pressures range beyond physiological pressures.

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Biomarker may detect RCC 5 years before diagnosis

Marker predictive of disease even in patients with good prognosis

Cheryl Guttman Krader
UT Contributing Editor

The protein Kidney Injury Molecule 1 (KIM-1) shows promise as a blood-based biomarker for renal cell carcinoma (RCC) diagnosis and for predicting overall survival after RCC diagnosis, according to findings of a recently published study.

“KIM-1 might increase the proportion of cases diagnosed with localized, curable disease.”

RUPAL S. BHATT, MD, PhD

Analyzing data obtained from participants in the European Prospective Investigation into Cancer and Nutrition (EPIC), a population-based, prospective cohort study, the research found a strong significant association between pre-diagnostic plasma concentration of KIM-1 and the risk of being diagnosed with RCC in the following 5 years. Furthermore, incorporating information about KIM-1 concentration approximately doubled the sensitivity of a model for predicting RCC risk.

In addition, the study, which was published in Clinical Cancer Research (July 23, 2018 [Epub ahead of print]), found an association between elevated pre-diagnostic plasma KIM-1 concentration and risk of death among RCC cases.

“Nephron-sparing nephrectomy is associated with high cure rates for patients diagnosed with localized RCC, but the prognosis remains poor for patients with more advanced disease. Identifying a sensitive and specific biomarker for detecting RCC at an early stage could improve overall survival,” said study author Rupal S. Bhatt, MD, PhD, associate professor of hematology and oncology, Harvard Medical School, and medical oncologist at Beth Israel Deaconess Medical Center, Boston.

“We have shown that plasma concentrations of KIM-1 are predictive of RCC up to 5 years prior to diagnosis, even among patients with a good prognosis. Thus, KIM-1 might increase the proportion of cases diagnosed with localized, curable disease. Now, further studies are needed, including research to determine when plasma KIM-1 becomes elevated prior to RCC diagnosis and if it is elevated before initial neoplastic changes occur,” Dr. Bhatt added.

Interest in the potential role of KIM-1 as a sensitive and specific blood biomarker for RCC diagnosis arose from previous studies showing that its plasma concentration was high in patients with clear cell RCC at the time of diagnosis, decreased significantly following nephrectomy, and accurately discriminated the RCC cases from healthy controls.

“It was not known, however, whether the plasma concentration of KIM-1 was elevated prior to RCC diagnosis,” said Dr. Bhatt.

To answer that question, the authors analyzed KIM-1 concentrations measured in plasma samples from 190 RCC cases and 190 controls. The selected cases had entered EPIC and donated blood up to 5 years prior to having a histologically confirmed diagnosis of RCC. Each case was matched to a control based on date of birth, date of blood donation, sex, and country of residence as matching criteria. Selected controls were cancer free except for non-melanoma skin cancer.

KIM-1 was detectable in the plasma samples from 93% of the cases and 70% of the controls. The median KIM-1 concentration was 2.5-fold higher in the cases compared with the controls (149 pg/mL vs. 59 pg/mL).

Potential use in high-risk populations

Associations between plasma KIM-1 concentrations and RCC risk and survival were analyzed using conditional logistic regression and flexible parametric survival models. Results showed each doubling in KIM-1 concentration corresponded to a 1.71 incidence rate ratio of RCC.

The increase in risk associated with an elevated KIM-1 concentration was similarly high whether considering cases diagnosed within 2 years of the plasma draw or those diagnosed 2 to 5 years thereafter.

It also persisted in an analysis that included only RCC cases with good prognosis, suggesting the potential utility of KIM-1 concentration for predicting early-stage RCC.

The authors noted that because the risk of RCC in the general population is low, an assay for plasma KIM-1 probably does not have a role as a screening test. Additionally, KIM-1 is elevated in patients with benign kidney disease, so this needs to be taken into consideration.

“More likely, it might be applied in high-risk populations or used as an adjunct to other diagnostics, Dr. Bhatt said.

In addition to Dr. Bhatt, co-authors include co-first authors David Muller, PhD, and Ghislaine Scelo, PhD, as well as Venkata Sabbisetti, PhD, and Joseph V. Bonventre, MD, PhD.

The study’s authors received honoraria for an advisory role and/or grants/reimbursements for participation in scientific events from Bristol-Myers Squibb. Dr. Kutikov has been a speaker for Pfizer.
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**Clinical Updates**

**OVERACTIVE BLADDER / No significant comorbidity difference in younger vs. older cohorts**

**Study: OnabotulinumtoxinA injections found safe in elderly patients**

Laird Harrison
UT Correspondent

SAN FRANCISCO—OnabotulinumtoxinA (onabotA) injection is safe to treat overactive bladder in patients 80 years of age and older, researchers say.

“Urinary tract infections are no more common in this population than in younger people, according to Patricia M. Zahner, MD, fellow in female pelvic medicine and reconstructive surgery at Cleveland Clinic. She presented the study at the AUA annual meeting in San Francisco.

“We treat a lot of elderly patients with Botox and it’s effective,” she told Urology Times.

OnabotA injections are common third-line treatments for overactive bladder. But some providers may be afraid to use them in elderly patients because of the most common adverse events: urinary retention and urinary tract infections.

“We worry that they may get more sick,” said Dr. Zahner, who worked on the study with Howard B. Goldman, MD, and colleagues.

To examine the risks of this treatment in older patients, the authors retrospectively reviewed the records of a series of patients who underwent onabotA injections for overactive bladder from 2007 to 2017. They compared 62 patients with a mean age of 84 years, ranging from 80-94 years, to 68 patients with a mean age of 59 years, ranging from 50-70 years.

There was no significant difference in comorbidities between the two cohorts (65% in the younger cohort and 76% in the elderly cohort, p=.24), or in reported satisfaction (p=.31).

Significantly more of the younger patients (53%) had neurologic conditions than the older patients (29%), p=.006.

Complication rates not statistically different

The overall rate of complications for the younger patients was 16% versus 23% for the older patients, but this difference did not reach statistical significance (p=.36).

The rate of urinary tract infections among the younger patients was 7.6% versus 6.5% among the elderly cohort. This difference also was not statistically significant (p=.84).

The rate of catheterization was 4.4% among the younger patients. None of these patients had an underlying neurologic condition. Among the younger patients who were catheterized, two patients had 100 units of onabotA. One had 200 units. All three were women with a history of prior incontinence surgery.

Among the older patients, 11% had catheterization, but the difference in catheterization between the younger and older cohorts was also not statistically significant (p=.14).

Two of the seven older patients with urinary retention had neurologic conditions. Five had 100 units. Two had 200 units. Three were men and four were women.

“So octogenarians might not be willing to catheterize, so there are pros and cons,” said Dr. Zahner.

Hematuria affected 4.4% of the younger patients and 1.6% of the older ones (p=.36). There were 10 unscheduled phone calls for the younger patients and 17 for the older patients (p=.22).

Unscheduled office visits and re-hospitalization rates were both more common in the older patients, but not significantly so. Pain was reported by 5.1% of the younger patients and none of the older patients, but this was also not statistically significant (p=.73).

Regardless of age, those with the most severe comorbidities were the most likely to be re-hospitalized (odds ratio: 16.1, [p=.01]), UT.

Ablation of trigone shows promise in treating OAB

No long-term adverse events observed, data show

John Schieszer
UT Correspondent

SAN FRANCISCO—Radiofrequency (RF) selective ablation of the trigone may be a promising approach for treating overactive bladder (OAB) patients with urgency urinary incontinence (UUI).

Researchers in a collaborative group reported that contiguous ablations across the trigone leads to effacement of nerves into the paravaginal space and appears to provide a therapeutic response while maintaining patient safety. The findings were presented at the AUA annual meeting in San Francisco.

“The majority of the procedures, three-quarters, were done essentially under sedation anesthesia and there were some patients who did require general anesthesia,” said study investigator Roger Dmochowski, MD, MMHC, professor of urologic surgery at Vanderbilt University Medical Center, Nashville, TN. “The number of ablations ranged from three to six in both groups.”

Dr. Dmochowski and his co-authors compared the efficacy and safety of two different ablation modalities and determined the duration of action with an investigational new treatment for OAB using the Silensa system. Manufactured by Amphora Medical, Inc. in Minneapolis, it uses RF energy to selectively ablate the nerve-rich layers of the deep detrusor and adventitial space beneath the trigone.

Dr. Dmochowski said this selective bladder denervation targets nerves which contribute to OAB symptoms (urgency and UUI) while sparing the bladder urothelium, vaginal mucosa, and surrounding pelvic viscera. The multicenter study was conducted in Canada and Belgium and it included 63 female patients

“Please see ABLATION, on page 13

“There is apparent promise here. There appears to be stability of results in those patients followed up over time.”

ROGER DMOCHOWSKI, MD, MMHC
Live demos of prostate procedure found safe

**Laird Harrison**
UT Correspondent

**SAN FRANCISCO**—Performing green laser enucleation of the prostate with a live audience does not result in more complications, researchers say.

The finding could ease concerns about the live demonstrations of surgical procedures, said Vincent Misrai, MD, a urologic surgeon at Clinique Pasteur in Toulouse, France. He presented the research at the AUA annual meeting in San Francisco.

Surgeons often demonstrate procedures, including green laser enucleation of the prostate, in front of students or other surgeons who are trying to learn the procedure. But some worry about patient safety.

“It puts pressure on the surgeon,” Dr. Misrai told *Urology Times*. “When you do the case, you speak, and while you speak, you lose time.”

Green laser enucleation of the prostate, first described in 2013, provides a good opportunity to study this effect because of the interest in live demonstrations and because of the demands of the procedure.

“When you proceed to the morcellation, it has to be done with clear vision and a trained scrub team to avoid complications such as bladder injuries,” Dr. Misrai explained.

To test the risk of complications with and without an audience, Dr. Misrai and his colleagues retrospectively reviewed the records of 126 patients who underwent a green laser enucleation at Clinique Pasteur between June 2015 and January 2017.

**“Every surgeon involved in surgical workshop programs should do the same evaluation to make sure of patient safety.”**

VINCENT MISRAI, MD

Of these, 37 procedures were performed during 17 live case demonstrations, including video of an endoscopic view and an external view of the operating room, with a median of three attendees.

The surgeon discussed each step of the procedure and responded to questions from the attendees, some of whom were in the theater while other attendees were in another room. The procedures were performed by the same surgeon in Group A and B.

Dr. Misrai and his colleagues retrospectively reviewed the records of 126 patients who underwent a green laser enucleation at Clinique Pasteur between June 2015 and January 2017.

**FIGURE: Green laser enucleation complication rates: Live audience vs. standard**

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Dr. Misrai and his colleagues retrospectively reviewed the records of 126 patients who underwent a green laser enucleation at Clinique Pasteur between June 2015 and January 2017.
Indication and Important Safety Information

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

Important Safety Information

Warnings and Precautions

Seizure occurred in 0.4% of patients receiving XTANDI in clinical studies. In a study of patients with predisposing factors for seizure, 2.2% of XTANDI-treated patients experienced a seizure. Patients in the study had one or more of the following pre-disposing factors: use of medications that may lower the seizure threshold; history of traumatic brain or head injury, cerebrovascular accident or transient ischemic attack, Alzheimer's disease, meningioma, or leptomeningeal disease from prostate cancer, unexplained loss of consciousness within the last 12 months, history of seizure, presence of a space occupying lesion of the brain, history of arteriovenous malformation, or history of brain infection. It is unknown whether anti-epileptic medications will prevent seizures with XTANDI. Advise patients of the risk of developing a seizure while taking XTANDI and of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

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

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

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

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

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

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

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

- therapy vs 14.7 months (95% CI, 14.2-15.0) with placebo + LHRH
- years (36.6 months [95% CI, 33.1-NR]) with XTANDI + LHRH

**Metastatic CRPC:** 23% reduction in the risk of death with XTANDI + LHRH therapy vs placebo + LHRH therapy (HR = 0.17 [95% CI, 0.14-0.21]; P < 0.0001). As seen in the PREVAIL trial:

- therapy vs placebo + LHRH therapy (HR = 0.17 [95% CI, 0.14-0.21]; P < 0.0001)

Castration-resistant prostate cancer is defined as disease progression on androgen deprivation therapy (LHRH therapy or prior bilateral orchiectomy). a CI, confidence interval; HR, hazard ratio; LHRH, luteinizing hormone-releasing hormone; NR, not reached; PSA, prostate-specific antigen.

1 Or after bilateral orchiectomy. b The primary endpoint of the study was metastasis-free survival, defined as the time from randomization to whichever of the following occurred first: 1) loco-regional and/or distant radiographic progression per BICR (blinded independent central review) or 2) death up to 112 days after treatment discontinuation without evidence of radiographic progression. c

**Drug Interactions**

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

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

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

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


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

CONTRAINDICATIONS
None.

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

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

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

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

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

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

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

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

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

Embryo-Fetal Toxicity
The safety and efficacy of XTANDI® have not been established in females. Based on animal reproductive studies and mechanism of action, XTANDI® can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraceptive methods while receiving XTANDI®. Advise females who are pregnant or may become pregnant.

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

Four randomized controlled clinical trials enrolled patients with CRPC that had progressed on androgen deprivation therapy and all seizure events resolved.

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

AFFIRM (NCT00974311; XTANDI® versus Placebo in Metastatic CRPC Following Chemotherapy)
AFFIRM enrolled 1199 patients with metastatic CRPC who had previously received docetaxel. The median duration of treatment was 8.3 months with XTANDI® and 3.0 months with placebo. During the trial, 48% of patients on the XTANDI® arm and 46% of patients on the placebo arm received glucocorticoids.

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

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

Table 1. Adverse Reactions in AFFIRM

<table>
<thead>
<tr>
<th>Category</th>
<th>XTANDI® N = 900</th>
<th>Placebo N = 399</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal Cord Compression and Cauda Equina Syndrome</td>
<td>7.4 (6.6)</td>
<td>4.5 (3.8)</td>
</tr>
<tr>
<td>Benign Impairment Disorders²</td>
<td>4.3 (0.3)</td>
<td>1.8 (0.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6.6 (0.0)</td>
<td>4.5 (0.0)</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot Flush</td>
<td>20 (10.0)</td>
<td>9 (5.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6.4 (2.1)</td>
<td>2.8 (1.3)</td>
</tr>
<tr>
<td><strong>Neurological System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td>12 (6.2)</td>
<td>5.5 (2.8)</td>
</tr>
<tr>
<td><strong>Infections and Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Respiratory Tract Infection³</td>
<td>11 (0.0)</td>
<td>6.5 (0.3)</td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>8.8 (0.0)</td>
<td>6.0 (0.5)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>6.5 (0.3)</td>
<td>4.0 (0.0)</td>
</tr>
<tr>
<td><strong>Renal and Urinary Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td>6.9 (1.8)</td>
<td>4.5 (1.0)</td>
</tr>
<tr>
<td>Pollakiuria</td>
<td>4.8 (0.0)</td>
<td>2.5 (0.0)</td>
</tr>
<tr>
<td><strong>Injury, Poisoning and Procedural Complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>4.6 (1.3)</td>
<td>1.3 (0.0)</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>3.6 (1.3)</td>
<td>1.0 (0.0)</td>
</tr>
<tr>
<td><strong>Respiratory Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>3.3 (0.1)</td>
<td>1.3 (0.3)</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>XTANDI N = 871</th>
<th>Grade 1-4 (%)</th>
<th>Grade 3-4 (%)</th>
<th>Placebo N = 844</th>
<th>Grade 1-4 (%)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenic Conditions</td>
<td>47</td>
<td>3.4</td>
<td>33</td>
<td>2.8</td>
<td>12</td>
<td>0.2</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Adverse Reactions in PREVAIL

Table 3. Adverse Reactions in TERRAIN

TERRAIN (NCT0288911): XTANDI versus Bicalutamide in Chemotherapy-naive Metastatic CRPC

TERRAIN enrolled 375 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 372 received at least one dose of study drug. The median duration of treatment was 11.6 months with XTANDI and 3.8 months with bicalutamide. Discontinuations with an adverse event as the primary reason were reported for 7.6% of XTANDI-treated patients and 6.3% of bicalutamide-treated patients. The most common adverse reactions leading to treatment discontinuation were back pain and pathologic fracture, which occurred in 3.6% of XTANDI-treated patients, and in 2.1% and 1.6% of bicalutamide-treated patients, respectively. Table 3 shows overall and common adverse reactions (>10%) in XTANDI-treated patients.

Table 3. Adverse Reactions in TERRAIN

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

PROSPER enrolled 1401 patients with non-metastatic CRPC, Grade 1-4 neutropenia occurred in 15% of patients receiving XTANDI (1% Grade 3-4) and in 6% of patients receiving placebo (0.5% Grade 3-4).

Table 4. Adverse Reactions in PROSPER

Laboratory Abnormalities

In the AFFIRM and PREVAIL studies in metastatic CRPC, Grade 1-4 neutropenia occurred in 15% of patients receiving XTANDI (1% Grade 3-4) and in 6% of patients receiving placebo (0.5% Grade 3-4). Table 5 shows laboratory abnormalities that occurred in ≥ 5% of patients, and more frequently (>2%) in the XTANDI arm compared to placebo in the PROSPER study.

Table 5. Laboratory Abnormalities in PROSPER
In the AFFIRM and PREVAIL studies in metastatic CRPC, hypertension was reported in 11% of patients receiving XTANDI and 4% of patients receiving placebo. Medical history of hypertension was balanced between arms. Hypertension led to study discontinuation in 1% of patients in each arm. In the PROSPER study in non-metastatic CRPC, hypertension was reported in 12% of patients receiving XTANDI and 5% of patients receiving placebo.

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

Gastrointestinal Disorders: vomiting

Neurological Disorders: posterior reversible encephalopathy syndrome (PRES)

Drug interactions

Drugs that Inhibit CYP2C8

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

Drugs that Induce CYP3A4

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

Effect of XTANDI on Drug Metabolizing Enzymes

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

Data

Animal Data

In an embryo-fetal developmental toxicity study in mice, enzalutamide caused developmental toxicity when administered at oral doses of 10 or 30 mg/kg/day throughout the period of organogenesis (gestational days 6-15). Findings included embryo-fetal lethality (increased post-implantation loss and resorptions) and decreased anogenital distance at ≥ 10 mg/kg/day, and cleft palate and absent patellae bone at 30 mg/kg/day. Doses of 30 mg/kg/day caused maternal toxicity. The doses tested in mice (1, 10 and 30 mg/kg/day) resulted in systemic exposures (AUC) approximately 0.04, 0.4 and 1.1 times, respectively, the exposures in patients. Enzalutamide did not cause developmental toxicity in rabbits when administered throughout the period of organogenesis (gestational days 6-18) at dose levels up to 10 mg/kg/day (approximately 0.4 times the exposures in patients based on AUC). In a pharmacokinetic study in pregnant rats with a single oral 30 mg/kg enzalutamide administration on gestation day 14, enzalutamide and/or its metabolites were present in the fetus at a Cmax that was approximately 0.3 times the concentration found in maternal plasma and occurred 4 hours after administration.

Lactation

Risk Summary

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

Data

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

Females and Males of Reproductive Potential

Contraception

Males

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

Infertility

Males

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

Pediatric Use

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

Geriatric Use

Of 2784 patients who received XTANDI in four randomized controlled clinical trials, 79% were 65 and over, while 36% were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Patients with Renal Impairment

A dedicated renal impairment trial for XTANDI has not been conducted. Based on the population pharmacokinetic analysis using data from clinical trials in patients with metastatic CRPC and healthy volunteers, no significant difference in enzalutamide clearance was observed in patients with pre-existing mild to moderate renal impairment (30 mL/min ≤ creatinine clearance [CrCl] < 60 mL/min) compared to patients and volunteers with baseline normal renal function (CrCl ≥ 90 mL/min). No initial dosage adjustment is necessary for patients with mild to moderate renal impairment. Severe renal impairment (CrCl < 30 mL/min) and end-stage renal disease have not been assessed.

Patients with Hepatic Impairment

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

OVERDOSAGE

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Administration of enzalutamide to male and female rasH2 transgenic mice by oral gavage daily for 26 weeks did not result in increased incidence of neoplasms at doses up to 20 mg/kg/day.

Enzalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either the in vitro mouse lymphoma thymidine kinase (TK) gene mutation assay or the in vivo mouse micronucleus assay.

Based on nonclinical findings in repeat-dose toxicity studies, which were consistent with the pharmacological activity of enzalutamide, male fertility may be impaired by treatment with XTANDI. In a 26-week study in rats, atrophy of the prostate and seminal vesicles was observed at ≥ 30 mg/kg/day (equal to the human exposure based on AUC). In 4-, 13-, and 39-week studies in dogs, hypogonadotropism 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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Pfizer Inc., New York, NY 10017

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076-3717-PM
Blood test may predict BCG treatment failures

Lisette Hilton
UT Correspondent

A simple blood test, much like that used to detect tuberculosis, might identify as many as half of bladder cancer patients likely to fail intravesical bacillus Calmette-Guérin (BCG) immunotherapy, according to a small study of high-risk nonmuscle-invasive bladder cancer patients.

About one-third of high-risk nonmuscle-invasive bladder cancer patients experience BCG treatment failure. But physicians treating these patients do not have access to a proven way to predict who will benefit versus fail before administering BCG treatment.

Being able to identify treatment failures before beginning BCG is important on many fronts, according to study author Florian Kern, MD, chair of immunology at Brighton and Sussex Medical School, Brighton, United Kingdom. “These patients will ultimately have lost valuable time while on BCG immunotherapy. They might have had side effects, as well, and their hopes will be dashed several months into the treatment course. A treatment that works better for them will have been delayed. This might shorten overall survival,” Dr. Kern told Urology Times.

The test seemed to immediately identify about 50% of the patients who would not have benefited from BCG treatment. Overall, the test correctly predicted recurrence-free survival in bladder cancer patients, with 79% sensitivity, 86% specificity, and overall correct classification in 78.6% of cases.

“The simplicity of our new test makes it very attractive as a clinical test. There are several tests for tuberculosis that are ultimately based on the same test principle and have been rolled out across the world in recent times,” Dr. Kern said in a press release.

How complication rates compared
The complication rate was 18.9% in the live case demonstrations and 24.7% in the standard procedures. The rates were also similar when the complications were broken down by severity using the Clavien-Dindo Classification system.

In the live case demonstrations, there were four cases of acute urinary retention, four cases of hematuria, and one case of urinary tract infection. In the standard condition group, there were seven cases of acute urinary retention, three cases of hematuria, one case of fever, one case of pain, three cases of urinary tract infection, two cases of other infection, one case of hematuria with recatheterization, and four cases of endoscopic clot removal.

There were no statistically significant differences between the two groups at 1 month, 3 months, or 6 months of follow-up.

At 1 month, the IPSS was 8 in both groups. The residual prostate volume was 20 mL in the live case group and 25 mL in the standard condition group. The rate of urinary incontinence was 16.2% in the live case group and 13.5% in the standard condition group.

At 6 months, the IPSS was 4 in both groups. PSA was 0.5 ng/dL in the live case group and 0.6 ng/dL in the standard condition group. None of the patients had urinary incontinence. The rate of unplanned readmissions was 8.1% in the live case group versus 17.9% in the standard condition group.

Dr. Misrai pointed out that he carried out the procedures in his own operating theater. “It is less difficult than when you are in another theater with teams you don’t know,” he said. Nevertheless, he said, doing this study reassured him that his teaching wasn’t harming his patients.

“Every surgeon involved in surgical workshop programs should do the same evaluation to make sure of patient safety,” he said.

FLORIAN KERN, MD

Detecting these patients before starting BCG therapy will allow providers and patients to make more informed choices about treatment, the authors concluded.

“The simplicity of our new test makes it very attractive as a clinical test. There are several tests for tuberculosis that are ultimately based on the same test principle and have been rolled out across the world in recent times,” Dr. Kern said in a press release.

However, it’s not yet time for urologists and others to withhold BCG, which is today’s standard treatment for preserving the bladder in these patients post resection.

“This was a pilot study. We are hoping to do a bigger confirmatory study soon to prove that the test is reliable,” Dr. Kern said. “Once the results are confirmed, the test may be rolled out widely. At this time, however, these are results that require confirmation before they are applied to clinical management.”

The blood test, which measures release of the pro-inflammatory molecule Interleukin-2 (IL-2) from immune cells, is similar to the test used to detect immune response to tuberculosis, widely used in tuberculosis testing.

79% sensitivity, 86% specificity
The authors found a tuberculin-induced, secreted IL-2 concentration of more than 250 pg/mL best predicted recurrence-free survival in bladder cancer patients.

The authors concluded.

“The simplicity of our new test makes it very attractive as a clinical test.”

Clinical Updates

LIVE DEMOS
continued from page 13

were conducted according to European Association of Urology policy.

The baseline ages, comorbidities, and body mass indices of the 37 patients who underwent surgery in live case demonstrations were similar to those of the 89 patients treated under standard conditions.

The prostate volume, antiplatelet or oral anticoagulation medication use, International Prostate Symptom Score (IPSS), Qmax, and rate of indwelling catheter use were also similar in both groups.

During the procedure, the total energy used, morcellation time, and catheterization time were similar as well. Operative time was slightly longer, but the difference was not statistically significant.
Q&A / PELVIC PAIN AND LUTS

Large datasets shed light on benign urologic conditions

Large research initiatives such as the MAPP (Multidisciplinary Approach to Chronic Pelvic Pain) Research Network and LURN (Symptoms of Lower Urinary Tract Dysfunction Research Network) seek greater understanding of conditions including urologic chronic pelvic pain syndrome, LUTS, nocturia, and more. In this interview, J. Quentin Clemens, MD, who is a researcher for both networks, discusses the research conducted by these groups and what practicing urologists can learn from their findings.

Q: Please discuss the MAPP Research Network and the work it is doing.
A: Both the MAPP (Multidisciplinary Approach to Chronic Pelvic Pain) Research Network and the LURN (Symptoms of Lower Urinary Tract Dysfunction Research Network) are funded by the National Institute of Diabetes and Digestive and Kidney Diseases. The NIDDK leadership identified a need for research groups to get together and study certain benign urologic conditions. The MAPP is focused on urologic pain conditions, which we’ve termed urologic chronic pelvic pain syndrome or UCPPS, and which refers to interstitial cystitis, bladder pain syndrome, and chronic prostatitis/chronic pelvic pain syndrome. It’s a six-site network that has essentially conducted cohort studies of these patients and a lot of very interesting analyses to try to better understand important subgroups.

Some of this work has involved looking at clinical data. For instance, we’ve identified that pain and urinary symptoms really are different concepts in that certain patients have more pain and certain patients have more urinary symptoms. Those don’t track very well together at all, either at baseline or longitudinally, so it suggests that there are two subgroups: pain patients and urinary symptom patients.

We see that clinically: You have some patients who urinate every 15 minutes, but they don’t say they have pain, and you have others who might have a lot of pain, but they may not urinate as frequently. We think that’s important because it will help us focus research on which treatments might improve which type of symptoms.

We’ve also done a lot of studies looking at neural imaging and experimental pain testing that have demonstrated that many patients have objective abnormalities, which is unique for pain syndromes in urology. This type of thing has been shown in other pain syndromes. But many patients have a centralized phenotype. In other words, they have not just pain in the pelvis but pain elsewhere in the body and hypersensitivity.

Please discuss what was gleaned from the LURN in regards to nocturia.
Q: Please tell me about the LURN network.
A: In some ways, the LURN has a more ambitious goal because it is studying a broader range of symptoms—essentially all of the non-painful urinary symptoms, so LUTS, overactive bladder, incontinence, etc. What that network has focused on is gathering baseline data, including a large volume of clinical data as well as post-void residual volumes, urinalyses, and physical exam data. Then, it uses complicated, state-of-the-art statistical methods to identify clusters of individual patients and compare those clusters to our traditional clinical phenotyping.

We’re finding differences and we’re not sure exactly what that means at this point, but the concept is that by using these computer techniques, we may be able to gain insight into differences in patients, which will in turn will give us insight into how to treat them differently.

Q: Is it fair to say that there are bladder-centric and non-bladder-centric pain syndromes?
A: I think so. The next step is to see how important this is. For instance, do certain types of patients respond better to certain therapies? That would tend to finalize the story that, yes, there are two different types of patients that we should treat differently.
We are following the patients out for a year, so we’ll be able to take the baseline data and see how that correlates with treatment response. There are different treatments that are prescribed by the LURN clinicians.

Q: What did you learn regarding male symptoms?
A: One potentially very important observation is the high rate of urinary incontinence that is reported. This is not just post-void dribbling; it seems like there’s a pretty high rate of urge incontinence as well. That’s a type of symptom that really is not assessed at all on the AUA Symptom Score, and our results suggest that it’s a more bothersome and prevalent symptom in men than what we might have otherwise thought.

Q: Did the LURN come up with a new symptom score to address this?
A: Yes. The first step has been to develop a very large, comprehensive symptom questionnaire that is not meant for clinical use. This is to identify potentially important subgroups and be very detailed in how the questions are done. However, we have done analysis of that and have come up with a shorter version that we are testing, and the plan is to have an instrument that is short but comprehensive that could potentially replace some of the existing instruments we have such as, possibly, the AUA Symptom Score.

Q: How about the female side? Any new caveats regarding female LUTS for practitioners to use?
A: The clustering analyses that we have done have focused a little more on women than men so far. What’s interesting is there’s a very severely impacted group that has a wide range of symptoms and seems to have a wide range of psychosocial abnormalities and other abnormalities as well. What that suggests is perhaps along the lines of some of the pain patients we see where there may be more of a need for multidisciplinary management of certain patients than others. So, again, this is very preliminary, but I think some very exciting new concepts will emerge related to female LUTS along those lines.

Q: Switching gears a little, mesh has been in the news a lot in recent years. Polypropylene mesh has been used in men for hernia repair for so long; why is it only controversial in females?
A: What’s interesting is it actually is somewhat controversial in men. There’s a fair bit of research in the general surgery literature that raises the question of not just pain but potential for systemic effects of the mesh similar to what’s been concerning in women. The FDA warning came out for female mesh and that has really highlighted a lot of the controversy and news about it, but there are questions about male mesh as well.

I was involved in research that looked at the New York state database and compared mesh patients with controls (Am J Obstet Gynecol 2017;216:495.e1-495.e7; Hernia 2017;21:637-42; J Urol 2017;198:884-9; Am J Surg 2016;216:481-6). We looked at men who had mesh for hernia repairs and women who had mesh for prolapse. We followed these patients out for 5-6 years and looked for the development of conditions like cancers and autoimmune diseases.

There was absolutely no effect. In fact, in some of the analyses, the mesh was protective, which of course is just a statistical thing. But the concept here is that there certainly can be local complications associated with mesh placement (pain, infection), but there is currently no compelling clinical evidence to support that mesh implantation causes systemic complications such as autoimmune disease or cancer.

Q: Evidence from a large dataset show an exposure rate of 3% to 10% in patients undergoing mesh placement without hysterectomy (Int J Womens Health 2015;7:331-43), but other factors could be involved, such as how the mesh is placed, the product versus the procedure, etc. Are we giving up on a good thing for a problem in a few?
A: I get your point and to some degree I agree in the sense that most people feel there probably is a place for mesh, but right now it’s not been well determined what that place is. There are registries. For instance, there’s a registry that the American Urogynecologic Society has put together working with the FDA to try to answer some of those questions.

I think the real concern is the possibility that mesh slings will be abandoned. The FDA warning specifically indicated that it was not referring to mesh slings, but rather was focusing on “mesh kits” for the treatment of pelvic prolapse. I think the data indicates that, compared to the alternative, which are autologous slings, mesh slings are less morbid and for most patients equally effective.

Q: You were the chair of the AUA’s Data Committee. Please discuss the AUA’s data-gathering efforts and how they are of benefit to practicing urologists.
A: There are two main areas the committee has focused on. The first is the AUA Census, and we’ve already seen some benefits of participating in that related to topics such as advanced practice provider use and burnout in urology where this information can provide good ammunition to improve certain aspects of urology practice. The fact is that people with data tend to be the ones that run the discussion, so participating in the census should be viewed as something that could help all of urology and in particular practicing urologists.

The second is the AUA Quality Registry, which is a tool that can help practitioners meet many of the CMS requirements related to MACRA and MIPS. Very soon, urologists are going to see their Medicare pay cut if they don’t participate in these CMS programs. With AQUA, the AUA has set up an infrastructure to help make the process as easy as possible, and this includes having measures that are specific to urology as opposed to measures that are very tangential, such as tobacco cessation and hypertension management.

Q: Please briefly discuss the issue of bacteriuria and clean intermittent catheterization.
A: It’s a huge problem because it leads to over-treatment of patients, and we are becoming more and more aware of the risk of over-use of antibiotics. Patients who use a catheter to empty their bladder will have bacteriuria, and it’s surprising to me how many clinicians don’t seem to be aware of that.

The problem, of course, is sometimes the symptoms are non-specific, in which case I recommend getting a urine culture and holding off on treating until the culture results are back and then seeing if the symptoms go away. If they do go away, then they shouldn’t get antibiotics.

Some patients do in fact have recurrent symptomatic UTIs, at which point I recommend checking for structural or functional abnormalities. What does that mean? I have them get a renal/bladder ultrasound to check for kidney stones or bladder stones and potentially urodynamics if they haven’t had that recently.

If all of that looks OK, we’ve had great success using intravesical gentamicin to help prevent UTIs. It can be administered each evening; patients instill 50 or 60 cc and then leave it in overnight and remove it the next morning when they’re catheterized. It does not cause gentamicin resistance and it works very well to reduce UTIs without exposing them to systemic antibiotics. I was a co-author of a study of this that was published in the Canadian Urological Association Journal (2017;11:E350-4).
Phase III RCC trial challenges current standard of care

Sunitinib found non-inferior to nephrectomy plus targeted therapy

In patients presenting with metastatic kidney cancer, cytoreductive nephrectomy along with immunotherapy (interferon, interleukin) has long been the standard of care due to the improved patient survival associated with this approach. However, a recent phase III trial demonstrated that anti-VEGF targeted therapy alone provided similar overall survival, without the need for cytoreductive nephrectomy (N Engl J Med 2018; 379:417-27).

The CARMENA trial aimed to study the benefit of initial nephrectomy followed by targeted therapy in patients with metastatic kidney cancer compared to targeted therapy (sunitinib [Sutent]) alone. The trial was designed to show that sunitinib alone was not inferior to the usual combination of nephrectomy plus sunitinib. Between September 2009 and September 2017, 450 patients with clear cell renal cell carcinoma, confirmed on mandatory biopsy, and metastatic disease were randomized 1:1 to receive nephrectomy-sunitinib or sunitinib alone. The median follow-up was 50.9 months.

The median overall survival in the sunitinib-alone group was longer (18.4 months) than in the nephrectomy-sunitinib group (13.9 months). In the overall survival analysis, the hazard ratio of death was 0.89 (95% CI: 0.71-1.10) in favor of the sunitinib-alone group, suggesting that this approach was “noninferior” to the combination of nephrectomy followed by sunitinib. In subgroup analysis, both the intermediate-risk and high-risk patients were noted to have longer median overall survival and lower hazard ratio of death in the sunitinib-alone group.

The median progression-free survival was similar amongst the sunitinib-alone group and the nephrectomy-sunitinib group (8.3 months vs. 7.2 months). Similarly, the objective response rate was comparable between the sunitinib-alone group (29.1%) and the nephrectomy-sunitinib group (27.4%).

Sunitinib-related grade 3 or 4 adverse events were reported by 32.8% in the nephrectomy-sunitinib group and 42.7% in the sunitinib-alone group (p=.04). Postoperative complications in the nephrectomy-sunitinib group, including Clavien-Dindo grade ≥III, were reported in 13 patients (6%).

Proper patient selection, including those with low-/intermediate-risk disease, is paramount.

It’s worth noting that randomized controlled trials are difficult to perform and often have to overcome significant challenges. Over a period of 8 years, the trial was open at 79 European centers that recruited, on average, less than one patient per year per site! Of the planned 576 patients, only 450 patients were recruited and the trial was closed early, after an interim analysis, due to slow recruitment.

Results contrary to those of previous studies

This trial challenges the current standard of care. These results are unexpected and are contrary to what had been learned through previous retrospective studies. The patient inclusion criteria appear to be different from some previous studies in that a large proportion of patients in the CARMENA trial were in the high-risk category (i.e., multiple adverse features). This may explain the lower-than-expected survival rate in these patients compared to other trials. It is difficult to explain the longer survival in the group without nephrectomy. It’s unlikely that removal of the primary tumor is resulting in poor survival, either due to some biologic effect or procedure related mortality. It’s likely an epiphenomenon related to trial design, patient accrual, and inclusion criteria.

In routine clinical practice, high-risk patients are not considered good candidates for cytoreductive nephrectomy because much of the benefit of cytoreductive nephrectomy has been noted in the intermediate-risk patients. In this trial, both the intermediate- and high-risk patients appear to have better outcomes without initial nephrectomy. However, slow accrual, early termination of the trial, and the lower-than-planned number of subjects can introduce confounders and reduce the statistical power of the study, especially when separately analyzing the outcomes of intermediate-risk and high-risk subgroups.

Cytoreductive nephrectomy as the standard of care was based on the two non-specific immunotherapy trials using cytokines (IL-2, interferon) reported in 2001. Since then, we have moved through several targeted agents (anti-VEGF, anti-mTOR) and have re-introduced immunotherapy in the form of immune checkpoint inhibitors (nivolumab [Opdivo], ipilimumab [Yervoy]). Can the results of CARMENA be extrapolated to the use of checkpoint inhibitors? Is it feasible to perform another randomized trial of checkpoint inhibitors, with or without nephrectomy?

As the authors correctly point out, a “one-size-fits-all” approach cannot be applied to patients with metastatic kidney cancer. Proper patient selection, including those with low-/intermediate-risk disease, is paramount. Reserving cytoreductive nephrectomy for those patients who have symptoms related to the primary tumor or those with favorable/intermediate risk criteria will help avoid unnecessary surgery and/or any delay in the initiation of systemic therapy.
TECENTRIQ®
THE FIRST FDA-APPROVED ANTI-PD1 CANCER IMMUNOTHERAPY

For locally advanced or metastatic urothelial carcinoma

Results for first-line, cisplatin-ineeligible patients¹

<table>
<thead>
<tr>
<th>CR</th>
<th>PR</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>23.5%</td>
<td>6.7%</td>
<td>16.8%</td>
</tr>
</tbody>
</table>

(n=28/19%; 95% CI, 16.2, 32.2)

MEDIAN DoR NOT REACHED
(range: 3.7, 16.6+)

IMvigor210 was a pivotal Phase II, multicenter, open-label, 2 cohorts trial that included a cohort of 119 patients with locally advanced or metastatic urothelial carcinoma who were ineligible for cisplatin containing chemotherapy and were either previously untreated or had disease progression at least 12 months after neoadjuvant or adjuvant chemotherapy. Patients received TECENTRIQ 200 mg IV q2w. Major efficacy endpoints included ORR assessed by IRF using RECIST v1.1 and DoR. Patients were considered cisplatin-ineligible if they met any one of the following criteria: impaired renal function (CrCl of 30 to 59 mL/min), ECOG PS of 2, hearing loss of ≥25 dB at 2 contiguous frequencies, or grade 2-4 peripheral neuropathy.²

³

CI-confidence interval; CR-complete response; CR/creatinine clearance; dB-decibels; DoR=duration of response; ECOC=Eastern Cooperative Oncology Group; IRF-independent review facility; IV=intravenous; ORR-overall response rate; PD-L1-programmed death ligand-1; PR=partial response; PS-performance status; q3w=every 3 weeks; RECIST=Response Evaluation Criteria in Solid Tumors.

*denotes censored value.

• Number of IRF assessed confirmed responders.

Immune-Mediated Endocrinopathies

- Hypothyroidism — Across clinical studies, Grade 2 hypothyroidism occurred in ≤1% of patients
- For Grade 2 to 4 hypothyroidism, initiate corticosteroids and hormone replacement therapy as clinically indicated

Other Immune-Mediated Adverse Reactions

- TECENTRIQ can cause severe or fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system
- Across clinical trials, cardiac, dermatologic, gastrointestinal, general, hematomal, musculoskeletal, neurological, ophthalmological, renal, and vascular immune-mediated adverse reactions occurred at an incidence of ≤1% in patients who received TECENTRIQ or were reported for other products in this class of therapy
- For suspected Grade 2 immune-mediated adverse reactions, exclude other causes and initiate corticosteroids as clinically indicated. For severe (Grade 3 or 4) adverse reactions, withhold TECENTRIQ and administer corticosteroids. Permanently discontinue TECENTRIQ for Grade 4 immune-mediated adverse reactions involving a major organ

Infections

- TECENTRIQ can cause severe infections including fatal cases
- Across clinical trials, infections occurred in ≥2% of patients, including Grade 3 (0.0%), Grade 4 (0.0%), and Grade 5 (0.1%) events
- Monitor patients for signs and symptoms of infection. For Grade 3 or 4 infections, withhold TECENTRIQ and resume once clinically stable

Infusion-Related Reactions

- TECENTRIQ can cause severe or life-threatening infusion-related reactions
- Across clinical trials, infusion-related reactions occurred in ≤1.5% of patients, including Grade 3 (0.2%) events
- Monitor for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion in patients with Grade 1 or 2 infusion-related reactions. Permanently discontinue TECENTRIQ in patients with Grade 3 or 4 infusion-related reactions

Embryo-Fetal Toxicity

- Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman. Verify pregnancy status of females of reproductive potential prior to initiating TECENTRIQ. Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months after the last dose

Nursing Mothers/Fertility

- Because of the potential for serious adverse reactions in breastfed infants from TECENTRIQ, advise female patients not to breastfeed while taking TECENTRIQ and for at least 5 months after the last dose

Most Common Adverse Reactions

The most common adverse reactions in cisplatin-ineligible UCa (rate ≥20%) were fatigue (52%), decreased appetite (24%), diarrhea (24%), and nausea (22%). The most common adverse reactions in previously treated UCa (rate ≥20%) were fatigue (52%), decreased appetite (26%), nausea (25%), urinary tract infection (22%), pyrexia (21%), and constipation (21%). You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.

Please see Brief Summary of Prescribing Information on adjacent pages.


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THE FIRST FDA-APPROVED ANTI-PD1 CANCER IMMUNOTHERAPY
5.5 Other Immune-Mediated Adverse Reactions

TECENTRIQ can cause severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system. While immune-mediated reactions usually manifest during treatment with TECENTRIQ, immune-mediated adverse reactions can also manifest after discontinuation of TECENTRIQ.

For suspected Grade 2 immune-mediated adverse reactions, exclude other causes and initiate corticosteroids as clinically indicated. For severe (Grade 3 or 4) adverse reactions, administer corticosteroids, prednisone 1 to 2 mg/kg/day or equivalents, followed by a taper. Interrupt or permanently discontinue TECENTRIQ based on the severity of the reaction [see Dosage and Administration (2.3)].

In clinical studies enrolling 2616 patients who received TECENTRIQ [see Adverse Reactions (6.1)], infections occurred in 42% of patients, Grade 3 (8.7%), Grade 4 (1.5%), and Grade 5 (1%). In patients with urothelial carcinoma, the most common Grade 3 or higher infection was urinary tract infections, occurring in 6.5% of patients in NSCLC, the most common Grade 3 or higher infection was pneumonia, occurring in 3.8% of patients.

5.7 Infusion-Related Reactions

TECENTRIQ can cause severe or life-threatening infusion-related reactions. Monitor for signs and symptoms of infusion-related reactions. Interrupt, slow the rate of, or permanently discontinue TECENTRIQ based on the severity [see Dosage and Administration (2.3)]. For Grade 1 or 2 infusion-related reactions, consider using pre-medications with subsequent doses.

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ [see Adverse Reactions (6.1)], infusion-related reactions resulted in 1.3% of patients, including Grade 3 (0.2%).

5.8 Embryo-Fetal Toxicity

Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman. There are no available data on the use of TECENTRIQ in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-10 pathway can lead to increased risk of immune-related adverse reactions of the developing fetus resulting in fetal loss.

Verify pregnancy status of females of reproductive potential prior to initiating TECENTRIQ. Advise females of reproductive potential to use a highly effective contraceptive method prior to treatment with TECENTRIQ and for at least 5 months after the last dose [see Use in Specific Populations (8.1, 8.3)].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

• Immune-Mediated Pneumonitis [see Warnings and Precautions (5.1)]
• Immune-Mediated Hepatitis [see Warnings and Precautions (5.2)]
• Immune-Mediated Colitis [see Warnings and Precautions (5.3)]
• Immune-Mediated Endocrinopathies [see Warnings and Precautions (5.4)]
• Other Immune-Mediated Adverse Reactions [see Warnings and Precautions (5.5)]
• Infections [see Warnings and Precautions (5.6)]
• Infusion-Related Reactions [see Warnings and Precautions (5.7)]

6.1 Clinical Trials 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.

The data described in the Warnings and Precautions section reflect exposure to TECENTRIQ in patients in two randomized, active-controlled, phase I/II studies, a phase I/II single arm study (PD494491g, M268210, BIRC, FR) which enrolled 524 patients with metastatic urothelial carcinoma, 1636 patients with metastatic NSCLC, and 456 patients with other tumor types. TECENTRIQ was administered at a dose of 1200 mg intravenously every 3 weeks in all studies except PD49491g. Among the 2616 patients, 36% were exposed for longer than 6 months and 20% were exposed for longer than 12 months.

The data described in this section were obtained from one open-label, single arm, multicohort study (M260215) and one randomized open-label, active-controlled study (G0A) in which TECENTRIQ was administered to 429 patients with locally advanced and metastatic urothelial carcinoma and 609 patients with metastatic NSCLC. In these trials, TECENTRIQ was administered at a dose of 1200 mg intravenously every 3 weeks.

Cisplatin-Ineligible Patients with Locally Advanced or Metastatic Urothelial Carcinoma

The safety of TECENTRIQ in patients with cisplatin-ineligible urothelial carcinoma was evaluated in M260215 (subset 1), a multicenter, open-label, single-臂 trial that included 119 patients with locally advanced or metastatic urothelial carcinoma who were ineligible for cisplatin-containing chemotherapy. Adverse reaction rates were similar compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical studies enrolling 2616 patients who received TECENTRIQ, Grade 2 or higher infusion-related reactions occurred in 6.5% of patients [see Adverse Reactions (6.1)]. Adverse reaction rates were generally similar in patients with urothelial carcinoma who were not enrolled in the cisplatin-ineligible subset. In patients who were eligible for cisplatin-containing chemotherapy, Grade 2 or higher infusion-related reactions occurred in 11.3% of patients [see Adverse Reactions (6.1)].
Table 2 summarizes the adverse reactions that occurred in ≥ 10% of patients and Table 3 summarizes Grade 3–4 selected laboratory abnormalities that occurred in ≥ 1% of patients treated with TECENTRIQ in IMvigor210 (Cohort 1).

Table 2: Adverse Reactions in ≥ 10% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 1)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TECENTRIQ N=119</th>
<th>All Grades (%)</th>
<th>Grades 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatiguea</td>
<td>52</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Peripheral edemaa</td>
<td>17</td>
<td>2</td>
<td></td>
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<tr>
<td>Pyrexia</td>
<td>14</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>22</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>16</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>15</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Abdominal painb</td>
<td>15</td>
<td>0.8</td>
<td></td>
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<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>24</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back/Neck pain</td>
<td>18</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>13</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>18</td>
<td>0.8</td>
<td></td>
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<tr>
<td>Rashc</td>
<td>17</td>
<td>0.8</td>
<td></td>
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<tr>
<td>Infections</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Urinary tract infectiond</td>
<td>17</td>
<td>5</td>
<td></td>
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<tr>
<td>Respiratory, Thoracic, and Mediastinal</td>
<td></td>
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<tr>
<td>Coughe</td>
<td>14</td>
<td>0</td>
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<tr>
<td>Dysemenf</td>
<td>12</td>
<td>0</td>
<td></td>
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<tr>
<td>Laboratory Abnormality</td>
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</tr>
<tr>
<td>Hyponatremia</td>
<td>15</td>
<td>10</td>
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<tr>
<td>Hyperglycemia</td>
<td>10</td>
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<td></td>
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<tr>
<td>Lymphopenia</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>7</td>
<td></td>
<td></td>
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<tr>
<td>Increased Alkaline Phosphatase</td>
<td>7</td>
<td></td>
<td></td>
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<tr>
<td>Increased Creatine</td>
<td>5</td>
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<tr>
<td>Hypophosphatemia</td>
<td>4</td>
<td></td>
<td></td>
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<tr>
<td>Increased ALT</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>3</td>
<td></td>
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<tr>
<td>Hematuria</td>
<td>3</td>
<td></td>
<td></td>
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<tr>
<td>Hyperkalemia</td>
<td></td>
<td></td>
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<tr>
<td>Hypoalbuminemia</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Previously Treated Patients with Locally Advanced or Metastatic Urothelial Carcinoma

The safety of TECENTRIQ was evaluated in IMvigor210 (Cohort 2), a multicenter, open-label, single-arm trial that included 310 patients with locally advanced or metastatic urothelial carcinoma who had disease progression during or following at least one platinum-containing chemotherapy regimen or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen (see Clinical Studies (14.1)). Patients received TECENTRIQ 1200 mg intravenously every 3 weeks until unacceptable toxicity, radiographic progression, or clinical progression or death. The median duration of exposure was 12.3 weeks (6.1 to 46 weeks).

The most common adverse reactions (≥ 20%) were fatigue, decreased appetite, diarrhea, dyspnea, anemia, edema, pyrexia, urinary tract infection, rash, hyperglycemia, nausea, vomiting, constipation, and hypothyroidism.

Table 3: Grade 3–4 Laboratory Abnormalities in ≥ 1% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 2)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grades 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremia</td>
<td>10</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>8</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
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<tr>
<td>Increased Alkaline Phosphatase</td>
<td>2</td>
</tr>
<tr>
<td>Increased Creatine</td>
<td>3</td>
</tr>
<tr>
<td>Increased AST</td>
<td>2</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>1</td>
</tr>
</tbody>
</table>

NSCLC

The safety of TECENTRIQ was evaluated in OAK, a multicenter, international, randomized, open-label trial in patients with metastatic NSCLC, who progressed during or following a platinum-containing regimen, regardless of PD-L1 expression (see Clinical Studies (14.2). A total of 609 patients received TECENTRIQ 1200 mg intravenously every 3 weeks until unacceptable toxicity, radiographic progression, or clinical progression or death. The study excluded patients with active or prior autoimmune disease or with medical conditions that required systemic corticosteroids. The study population characteristics included: median age of 63 years (25 to 85 years), 46% age 65 years or older, 62% male, 71% White, 20% Asian, 68% former smoker, 16% current smoker, and 63% had ECOS performance status of 1. The median duration of exposure was 3.4 months (0 to 26 months) in TECENTRIQ-treated patients and 2.1 months (0 to 23 months) in docetaxel-treated patients. The most common adverse reactions (≥ 20%) in patients receiving TECENTRIQ were fatigue (43.5%), decreased appetite (23.5%), dyspnea (22%), and cough (20.4%). The most common Grade 3–4 adverse reactions (≥ 2%) were dyspnea, pneumonia, fatigue, anemia, and pulmonary embolism.

TECENTRIQ was discontinued due to adverse reactions in 8% of patients. The most common adverse reactions leading to TECENTRIQ discontinuation were fatigue, infections and dyspnea. Fatal adverse reactions occurred in 1.6% of patients; these included pneumonia, sepsis, septic shock, dyspnea, pulmonary hemorrhage, sudden death, myocardial ischemia or renal failure. Adverse reactions leading to interruption of TECENTRIQ occurred in 25% of patients; the most common (≥ 1%) were pneumonia, liver function test abnormalities, dyspnea, fatigue, pyrexia, and back pain. Serious adverse reactions occurred in 33.5% of patients. The most frequent serious adverse reactions (≥ 1%) were pneumonia, sepsis, dyspnea, pleural effusion, pulmonary embolism, pyrexia and respiratory tract infection.

Table 4 summarizes adverse reactions that occurred in at least 10% of patients treated with TECENTRIQ. Table 5 summarizes selected laboratory abnormalities worsening from baseline that occurred in ≥ 20% of patients treated with TECENTRIQ.
In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data
Animal reproduction studies have not been conducted with TECENTRIQ to evaluate its effect on reproduction and fetal development. A literature-based assessment of the effects on reproduction demonstrated that a central function of the PD-L1/PD-1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to a fetus. Blockage of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to a fetus and to result in an increase in fetal loss; therefore, potential risks of administering TECENTRIQ during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-L1/PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in P-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to TECENTRIQ may increase the risk of developing immune-mediated disorders or altering the normal immune response.

8.2 Lactation
Risk Summary
There is no information regarding the presence of atezolizumab in human milk, the effects on the breastfed infant, or the effects on milk production.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing
Verify pregnancy status in females of reproductive potential prior to initiating TECENTRIQ [see Use in Specific Populations (8.1)].

Contraception
Females
Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman. Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment or interruption or discontinuation of TECENTRIQ, including:

• Pneumonia: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath [see Warnings and Precautions (5.1)].
• Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding [see Warnings and Precautions (5.2)].
• Colitis: Advise patients to contact their healthcare provider immediately for diarrhea, blood or mucus in stools, or severe abdominal pain [see Warnings and Precautions (5.3)].
• Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, hyperthyroidism, hypothyroidism, adrenal insufficiency, or type 1 diabetes mellitus, including diabetic ketoacidosis [see Warnings and Precautions (5.4)].
• Other Immune-Mediated Adverse Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of other potential immune-mediated adverse reactions [see Warnings and Precautions (5.5)].

Infections
Advise patients to contact their healthcare provider immediately for signs or symptoms of infection [see Warnings and Precautions (5.6)].

Infusion-Related Reactions
Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions [see Warnings and Precautions (5.7)].

Entero-Fetal Toxicity
Advise females of reproductive potential that TECENTRIQ can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.8)].

Lactation
Advise females not to breastfeed while taking TECENTRIQ and for at least 5 months after the last dose [see Use in Specific Populations (8.3)].

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.
Best apps to get urologists through their day

Versatile tools provide instant access to guidelines, journals, and more

Instant access to information via our mobile devices has become a daily necessity and has transformed how our modern world interacts. To help the modern urologist, we list and briefly review the best apps to get urologists at all levels of expertise through their day.

Our search was focused on apps available through the App Store (Apple) and Google Play (Android OS). Divided into major categories—guidelines, journal articles, management, and patient education tools—we list the apps relevant to our world that get the job done. Bold text indicates the terminology used to search for a given app.

Guidelines

AUA Guidelines at a Glance (App Store/Google Play) serves as a quick reference for urologists on the most current evidence-based clinical guidelines and best practice guidelines published by the AUA (figure 1). (Publisher: American Urological Association [AUA])

AUA University (App Store/Google Play) mirrors the AUA University website and includes access to the AUA Core Curriculum, which is a comprehensive reference divided into over 80 specialized sections. The app is a valuable tool for daily clinical practice and board exam preparation as it links to a number of resources, including webcasts, textbooks, videos, articles, and simulations. (Publisher: AUA)

EAU Pocket Guidelines App 2018 (App Store/Google Play) provides a quick and easy way to access the content of the 2018 European Association of Urology (EAU) guidelines, organized into over 20 topics that discuss management, investigation, diagnosis, and follow-up of various urologic conditions. There are free versions of the pocket guidelines available with initial app installation; EAU members can access the remainder of the pocket guidelines, while non-EAU members are required to purchase them. (Publisher: EAU)

SIU Academy App (App Store/Google Play) mirrors the Société Internationale d'Urologie (SIU) Academy eLearning portal with access to numerous educational activities, including ePosters, webcasts, expert opinion videos and editorials, CME-accredited courses, interactive quizzes with surgical videos, and e-grand rounds and endourology series. The app also allows users to search for content related to topics of interest. SIU Academy App is available to SIU members. (Publisher: SIU/Multilearning Group)

NCCN Guidelines for Smartphones (App Store/Google Play) allows providers to access the most up-to-date National Comprehensive Cancer Network (NCCN) algorithms and discussions for management decisions and interventions applicable to 97% of all patients with cancer. There are additional guidelines and pathways focused on prevention, screening, and supportive care. This app is available upon free registration at NCCN.org. (Publisher: TIP Medical Communications)

Literature search and journals

Major urology journals have also created apps to offer readers easy and quick access to current and archived editions. However, before entering a journal site, the most frequently used search engine for first finding a reliable academic reference remains Pubmed.com, which is accessible via the app PubMed4Hh (figure 2), offered by the National Library of Medicine, one of the most respected sources of established journal articles and references. However, to supplement the urologist's mobile library, the following apps provide easy access to key urology journals:

- **AUA Journals** (access to Journal of Urology and Urology Practice)
- **Urology, the Gold Journal**
- **BJUI Journal**
- **European Urology**
- **Reviews in Urology**
- **Neurourology and Urodynamics**
- **Urologic Oncology**

Please see **UROLOGY APPS**, page 28
UROLOGY APPS
continued from page 27

Other mobile management tools

**UpToDate** (App Store/Google Play) offers extensive evidence-based clinical information, including recommendations for management, opportunities to earn and track free CME/CE/CPTD credits, as well as patient education materials. (Publisher: UpToDate, Inc.)

**Epocrates**, an athenahealth service, and **Lexicomp** (App Store/Google Play) are two apps that contain information about pharmacology and dosing, as well as drug indications and guidelines for use, contraindications, side effects, and drug-drug interactions to enhance efficiency and safety in daily practice. The Epocrates app is free with the ability to upgrade to an Epocrates Plus subscription, which offers additional features, such as alternative medications, lab guides, and evidence-based disease treatment options by patient type (figure 3). New Lexicomp users will receive a 1-month free trial with the option to pay for continued access thereafter. (Publishers: athenahealth, Inc.; Lexicomp)

**Urological Emergencies** (App Store/Google Play) provides a systematic approach to the initial management, differential diagnosis, and treatment of common urologic emergencies, which is especially valuable for urologists in training. (Publisher: Brainydoc Ltd.)

**Oxford Handbook of Urology** (App Store/Google Play) allows users the opportunity to subscribe to the latest version of the Oxford Handbook of Urology. (Publisher: Indextra AB)

**CDC Antibiotic Guidelines and STD Tx Guide** (App Store) serve as guides for prevention, diagnosis, and treatment of sexually transmitted diseases (STDs), in addition to identification of at-risk populations. (Publisher: Paul Chan, Centers For Disease Control and Prevention)

**Mobile PDR** (App Store/Google Play) is the official drug information app from Physician Desk Reference (PDR), a longtime reference for drug prescribing information. (Publisher: PDR Network)

**Doximity** (App Store/Google Play) is a free app that connects physicians, nurse practitioners, physician assistants, and pharmacists. Each member has a Doximity profile, which provides access to HIPAA-secure fax and caller ID services, as well as clinical news. (Publisher: Doximity)

**Calculation tools**

**MDCalc Medical Calculator** (App Store/Google Play) provides 350-plus clinical calculators, risk scores, and algorithms that cover the entire spectrum of medicine (figure 4). FENA, creatinine clearance, CAPRA score, prostate volume, and PSA density are only a few calculations that are useful in daily urologic practice. (Publisher: MD Aware, LLC)

**Prostate Cancer Clinical Risk Classification Tool** (App Store) is a simple app that calculates a patient’s NCCN Risk Classification based on PSA, biopsy findings, and digital rectal examination findings. (Publisher: Genomic Health, Inc.)

**Patient education and self-management tools**

**drawMD – Patient Education** (App Store/Google Play) allows providers to use medical art with annotations to educate their patients about medical conditions and procedures with the assistance of personalized illustrations, presentations, and handouts (figure 5). (Publisher: Visible Health, Inc.)

**Kegel Nation** (App Store) incorporates a biofeedback feature that allows male and female patients to measure how often they perform their Kegel exercises and how long they spend contracting and relaxing their pelvic muscles during each exercise. The app also allows patients to track their urinary function, such as frequency of urinary urgency, number of trips to the bathroom, number of incontinence events, and number of urinary pads used. This app is valuable for gauging response to treatment and allows for implementation of timely intervention. (Publisher: UCSF)

**Bladder Pal 2** (App Store) allows patients to maintain a bladder diary by tracking their fluid intake and urinary output. It also contains AUA tests designed to help men assess the severity of their urinary symptoms and response to therapy. (Publisher: Ronald L. Yap, MD)

**Animated Atlas of BPH & OAB** (App Store/Google Play) illustrates the anatomy and physiology of the prostate gland and the urinary bladder, as well as the pathophysiology, diagnosis, and treatment of BPH and overactive bladder. This atlas serves as animated reference for effective presentations to patients and colleagues. Limited features can be accessed for free, and the remaining content must be purchased. (Publisher: Focus Medica India Pvt. Ltd.)

**Summary**

More and more urologists are using these apps as an educational and reference tool in their daily practice. The apps offer the ability to continuously access information and promote the dissemination of knowledge among physicians and patients.
PROSTATE-RECTUM SPACING DURING RADIATION THERAPY

Help Preserve Your Prostate Cancer Patients’ Quality of Life with SpaceOAR Hydrogel.

In the pivotal trial, SpaceOAR patients did not experience any Grade 2 or greater rectal adverse events (e.g. proctitis, rectal bleeding, or fecal incontinence).¹ ²

- In-office transperineal injection under local anesthesia
- New Category 1 CPT code - 55874 - effective January 1, 2018

To learn how you can integrate SpaceOAR hydrogel into your urology practice, go to www.spaceoar.com/aua

¹ From 3 months onward post radiotherapy [data on file]

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ICD-10: Beware of these three common coding mistakes

Errors related to bladder Ca site and symptom codes could lead to take backs

O ct. 1 marks the beginning of the fiscal year for the Centers for Medicare & Medicaid Services. This milestone does not include the changes in Medicare payments that occur with the implementation of new rules, CPT codes, or changes in the fee schedule. Those changes begin on Jan. 1 of each year, and we will once again provide you with updates in November once the final rule is published. Oct. 1 does, however, mark the new year for ICD-10.

The 2019 release includes 279 new codes, 51 deleted codes, and 143 revised codes. As of Oct. 1, 2018, there will be 71,932 active ICD-10 CM codes.

The table contains a list of the codes we have identified as new codes for urology. The changes are a reflection of needs identified by the World Health Organization and adapted for the U.S. under the guidance of the AUA.

Although these changes will not impact most urology practices daily, we encourage you to review them and make additions to your “favorites” lists and cheat sheets based on your practice.

Please see ICD-10 ERRORS, page 32

### TABLE: NEW UROLOGY-RELATED ICD-10 CODES FOR 2019

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>N35.016</td>
<td>Post-traumatic urethral stricture, male, overlapping sites</td>
</tr>
<tr>
<td>N35.116</td>
<td>Postinfective urethral stricture, not elsewhere classified, male, overlapping sites</td>
</tr>
<tr>
<td>N35.81</td>
<td>Other urethral stricture, male</td>
</tr>
<tr>
<td>N35.811</td>
<td>Other urethral stricture, male, meatal</td>
</tr>
<tr>
<td>N35.812</td>
<td>Other urethral bulbous stricture, male</td>
</tr>
<tr>
<td>N35.813</td>
<td>Other membranous urethral stricture, male</td>
</tr>
<tr>
<td>N35.814</td>
<td>Other anterior urethral stricture, male, anterior</td>
</tr>
<tr>
<td>N35.816</td>
<td>Other urethral stricture, male, overlapping sites</td>
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<tr>
<td>N35.819</td>
<td>Other urethral stricture, male, unspecified site</td>
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<tr>
<td>N35.82</td>
<td>Other urethral stricture, female</td>
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<tr>
<td>N35.91</td>
<td>Urethral stricture, unspecified, male</td>
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<td>N35.911</td>
<td>Unspecified urethral stricture, male, meatal</td>
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<td>N35.92</td>
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<tr>
<td>N99.116</td>
<td>Postprocedural urethral stricture, male, overlapping sites</td>
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<tr>
<td>R82.991</td>
<td>Hypocitraturia</td>
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<td>Hyperoxaluria</td>
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<td>R82.993</td>
<td>Hyperuricoscuria</td>
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<tr>
<td>R82.994</td>
<td>Hypercalcium</td>
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<tr>
<td>R82.998</td>
<td>Other abnormal findings in urine</td>
</tr>
<tr>
<td>R93.811</td>
<td>Abnormal radiologic findings on diagnostic imaging of right testicle</td>
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<tr>
<td>R93.812</td>
<td>Abnormal radiologic findings on diagnostic imaging of left testicle</td>
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<tr>
<td>R93.813</td>
<td>Abnormal radiologic findings on diagnostic imaging of testicles, bilateral</td>
</tr>
<tr>
<td>R93.819</td>
<td>Abnormal radiologic findings on diagnostic imaging of unspecified testicle</td>
</tr>
<tr>
<td>T81.44</td>
<td>Sepsis following a procedure</td>
</tr>
<tr>
<td>T81.49</td>
<td>Infection following a procedure, other surgical site</td>
</tr>
</tbody>
</table>

Source: Compiled from Centers for Medicare & Medicaid Services data by Ray Painter, MD, and Mark Painter

### BUSINESS SECTION

32 ■ PRACTICE MATTERS
Why your practice needs to track phone call quality

38 ■ MONEY MATTERS
401(k) with a previous employer: What are your options?
No refills necessary.

When BPH medications come up empty, give your patients a solution that lasts. Rezūm™ Water Vapor Therapy treats the problem, not just the symptoms, and gives your patients the freedom they had lost.

Effective: 11-point IPSS symptom improvement maintained through 3 years\(^1\)
Durable: 4.4% procedural retreatment rate at 3 years\(^1\)
Flexible: Ability to treat all areas of enlarged prostate tissue
QoL: Preserves sexual function\(^1,2\)
Convenient: In-office treatment removes the complexities of a hospital setting

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Contact us at info@rezum.com to learn more.


Why your practice needs to track phone call quality

Your ‘call center’ is key to a good first impression

Thank you for calling Urology Specialists of the Western Hemisphere. If this is an emergency, please hang up immediately and dial 9-1-1 or go to an emergency room. For prescription refills, please contact your pharmacy. Press 9 to…”

If this recorded greeting, which is unnecessary for most callers, sounds familiar, you may want to reevaluate how your practice manages the primary tool for patient engagement—the telephone call. Do you put your least experienced and lowest paid staff in this important role? Have you installed and configured phone systems that all but guarantee the first contact with the practice will not be a live voice or human touch?

These common responses to the pressures and pace of a contemporary specialty practice may ultimately shape the first impression of a patient or referring physician’s office, impact patient and provider satisfaction, and even determine customer loyalty. In this article, I will discuss the concept of a “call center” in a modern urology practice.

Call centers come in different shapes and sizes. If you have one or more employees answering your phone, your primary tool for patient engagement—the telephone call—should be a live voice engaged with the patient.

The other general area in which urologists need to improve their diagnosis reporting is for diseases that are chronic and/or affect the care or treatment that the patient either directly or indirectly. We have consistently taught in our seminars and articles that MIPS and the various other value-based medicine programs are looking at total cost of patient care. Your patient data risk and the statistical comparison of you and your practice to others is benchmarked to all the diagnoses a patient is assigned. Ignore these at your own peril.

We strongly recommend training your staff to assist you in coding for all relevant diagnoses for each patient, including updating any older diagnoses and adding new chronic diseases. It is often difficult to work into your daily encounters the time to add these diagnosis codes to the patient record as they typically do not have an effect on payment for that visit. But you need to understand that your long-term financial health can be adversely affected by these additional patient problems.

Add to your office work flow processes clear history forms and updates that allow you to collect this information and delegate to appropriate and well-trained staff the actions required to submit complete and accurate bills for each encounter.

ICD-10 coding is not easy if you approach each visit with a blank slate and try do all the work yourself; however, we have seen many practices develop and have assisted many others in developing processes that guide you to accurate bills with little disruption to your daily routine. UFT

A great example of a misused symptom code in urology is hematuria.

Using N40.1 even if the symptom is due to BPH as instructed in the ICD-10 coding manual.

In cases where the symptom is no longer present or a diagnosis has been established and the symptom is a manifestation of the disease, it should be removed from the active diagnosis list. A great example of a misused symptom code in urology is hematuria. Any diagnosis of hematuria with a urinalysis that is clear on the same date is incorrect unless, as noted above, the patient presents with a referral for hematuria with no other symptom or disease diagnosed. A patient with hematuria due to bladder cancer with a diagnosis of bladder cancer is also incorrect.

Cancer diagnosis assigned to a patient who has undergone surgical removal of the cancer with no symptoms of the disease present. Patients who have undergone treatment for prostate, testicular, kidney, or bladder cancer for which the cancer has been removed and in whom there is no elevated PSA, remaining cancerous tissue, etc., should be diagnosed with a personal history of malignant neoplasm. This method of reporting is not only incorrect from a coding standpoint, but it helps you in your patient treatment statistics in the payer databases.

The other general area in which urologists need to improve their diagnosis reporting is for diseases that are chronic and/or affect the care or treatment that the patient either directly or indirectly.
the phone during business hours, then you have a call center—whether you call it that or not. After hours, your answering service may be your “call center”—responsible for representing your practice in a professional and reliable way. Some large practices with multiple offices have centralized routing and distribution of some or all phone calls by staff in a dedicated physical space—a physical call center.

No matter the size of your practice or location of your “call center,” the needs of your callers are the same. One author summed it up nicely: “We want to be treated well, we want the human on the other end of the line to correctly pronounce our name, we want them to be friendly even when we’re not, and (most importantly) we want our problem solved” ([bit.ly/callcenterhistory]). The goal of your call center is to get the caller’s problem solved in a dignified, professional, and respectful manner. The call center is the face of your practice.

How to measure call center performance
Where do you begin in assessing the efficiency and quality of answering phone calls in your practice? There are basic measurements that can begin to answer this question and get you started. Many phone or call management systems have reporting capabilities. If you don’t have such a system, you may have to manually audit or observe the number of calls, the average length and type of calls (appointments, refills, medical concerns), the category of caller (new patient, established, physician, hospital, etc.), how many calls per hour your staff is completing, how many callers reach a human, and how many calls are abandoned.

The electronic health record may be an important secondary source of information as it may measure messages by provider, tasks, or refill requests. Interview one or more of your staff who answer the phones and get their perspective on what’s working and what is not working. If you measure patient satisfaction, drill down on any information related to experience on the phone; if you don’t measure satisfaction objectively, ask your patients about their experience interacting with the practice.

Go online to ratings sites and see if people are talking about your customer service. Call your practice posing as a new patient and see what happens. With minimal focused effort, you should be able to get a clear idea of whether there is an opportunity for improvement and how to target the solutions.

Just as you would not let your nurse administer BCG without proper training, you should work to ensure that the face of the practice—the call center—is properly trained and supervised.

How do you know what is normal performance for your call center? There are three common benchmarks or key performance indicators to use for comparison. First, the average abandonment rate is the percentage of calls that were disconnected before being answered. Second, the average time in queue is the amount of time after a call has been answered before the caller speaks to an agent. Finally, the average time to answer measures how long it took the agent to answer the call. According to one source, these benchmarks for health care are 13%, 2.5 seconds, and 3.2 seconds, respectively ([bit.ly/callcenterbenchmarks]). If you are far off these benchmarks—especially abandoned call ratio—then you may be losing business and not even know it.

Three avenues of solutions
Once you have identified the opportunities, you can begin to apply targeted solutions.

Reduce inbound calls. The first—and often overlooked—category of solutions is to prevent inbound phone calls to begin with and reduce the load on the staff. Do you have a patient portal, online bill pay, virtual scheduling, live chat, secure email, or alternatives that can eliminate the need for phone calls? Are you anticipating questions in your patient literature, especially when preparing for a procedure? Are you accurately maintaining patient email and phone information so your patient reminder system actually works? Does your refill policy generate more daytime calls than after hours calls it prevents?

Also consider these questions: Are you returning morning messages promptly to prevent a second or third call back? Have you considered a dedicated phone number for physicians and hospitals, instead of routing it through the call center? Do one or more of your providers review their inbound lab results daily? Are you monitoring your failed outbound electronic prescriptions or faxes? Addressing these and other opportunities will return dividends in your call center performance.

Assess your technology. The second major category of solutions is technology. If you don’t have a call management system, examine the economics and see if it makes sense—the return on investment should be tangible and significant in a busy practice of any size. If you do have a call management system, be sure it is properly configured to monitor and report call and staff activity. Examine settings in your appointment scheduling software to ensure the staff can easily find available appointment slots. Are the interfaces between systems working properly, or do the staff have to waste time with dual entry? Does the staff have access to all the systems they need (the EHR, for example)? Involve your IT staff in ensuring that some chronic problems in technology are not directly impacting your call center staff and customers.

Evaluate your staff and training. The third category of solutions is human resources. Just as you would not let your nurse administer BCG without proper training, you should work to ensure that the face of the practice—the call center—is properly trained and supervised. Some phone systems allow supervisors to monitor phone calls to assess the quality of calls, are they doing that? Do your staff know how to get the answers to basic common questions such as, “How long has Dr. Jones been in practice?” or “Does Dr. Smith take my insurance?” Are staff held accountable to some of the benchmarks mentioned above? Do you have the right people in the call center? The call center can be the nerve center of the practice, but may not be getting the attention it deserves.

Bottom line: The customer experience will increasingly differentiate high-performing medical practices, and the phone will be an enduring interface between your practice and your customers. Don’t assume that no news is good news—take a look at how your “call center” is working and see if you can answer some of these questions as well as your callers. UT
When kidneys work overtime to produce too much urine at night, think NOCTIVA

INDICATIONS AND USAGE
NOCTIVA is a vasopressin analog indicated for the treatment of nocturia due to nocturnal polyuria in adults who awaken at least 2 times per night to void.

Limitation of Use: Not studied in patients <50 years of age.

CONTRAINDICATIONS
NOCTIVA is contraindicated in patients with the following conditions: hyponatremia or a history of hyponatremia, polydipsia, primary nocturnal enuresis, concomitant use with loop diuretics or systemic or inhaled glucocorticoids, estimated glomerular filtration rate <50 mL/min/1.73 m², syndrome of inappropriate antidiuretic hormone secretion (SIADH), during illnesses that can cause fluid or electrolyte imbalance, congestive heart failure (New York Heart Association Class II-IV), and uncontrolled hypertension.

IMPORTANT SAFETY INFORMATION

WARNING: HYponatREMIA
See full prescribing information for complete boxed warning.

• NOCTIVA™ (desmopressin acetate) Nasal Spray can cause hyponatremia. Severe hyponatremia can be life-threatening, leading to seizures, coma, respiratory arrest, or death.

• NOCTIVA is contraindicated in patients at increased risk of severe hyponatremia. See Important Safety Information below for full contraindications.

• Ensure serum sodium is normal before starting or resuming NOCTIVA. Measure serum sodium within 7 days and approximately 1 month after initiating therapy or increasing the dose, and periodically during treatment. More frequently monitor patients ≥65 years of age and those at increased risk of hyponatremia.

• If hyponatremia occurs, NOCTIVA may need to be discontinued.
40 million patients in the US have nocturia,¹,² and in 80% of those cases, it’s caused by nocturnal polyuria,³ the overproduction of urine at night. NOCTIVA treats the problem at the source—in the kidneys.⁴

Through a patented formulation and delivery system administered via a once-nightly nasal spray⁴,⁵:

- NOCTIVA is available in 2 microdoses: 0.83 mcg and 1.66 mcg⁴
- NOCTIVA is rapidly and consistently absorbed within 15 (0.83 mcg) and 45 (1.66 mcg) minutes, depending on the dose³,⁴
- Nearly 50% of patients using NOCTIVA 1.66 mcg reduced the number of times they woke up to void by half or more⁴
- Patients experienced clinical effect on the first night of use⁵

To learn more about the first FDA-approved treatment for adults with nocturia due to nocturnal polyuria,⁴,⁶ visit www.NOCTIVAHCP.com/UT

WARNINGS AND PRECAUTIONS
- Fluid retention: Not recommended in patients at risk of increased intracranial pressure or history of urinary retention. Monitor volume status in patients with NYHA Class I congestive heart failure.
- Nasal conditions: Discontinue in patients with concurrent nasal conditions that may increase absorption, until resolved.

ADVERSE REACTIONS
Common adverse reactions in clinical trials (incidence >2%) included nasal discomfort, nasopharyngitis, nasal congestion, sneezing, hypertension, back pain, epistaxis, bronchitis, and dizziness.

DRUG INTERACTIONS
Monitor serum sodium more frequently when NOCTIVA is concomitantly used with drugs that may cause water retention and increase the risk for hyponatremia.

USE IN SPECIFIC POPULATIONS
- Pregnancy: Use of NOCTIVA is not recommended.
- Pediatric: Do not use NOCTIVA for primary nocturnal enuresis in children.

To report SUSPECTED ADVERSE REACTIONS, contact Avadel at 1-877-638-4579 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.


Please see Brief Summary of full Prescribing Information on next page.
NOCTIVA™ (desmopressin acetate) Nasal Spray

The following is a brief summary. Please consult Full Prescribing Information for complete details.

WARNING: HYponATREMIA
• NOCTIVA can cause hyponatremia. Severe hyponatremia can be life-threatening, leading to seizures, coma, respiratory arrest, or death.
• NOCTIVA is contraindicated in patients at increased risk of severe hyponatremia, such as patients with excessive fluid intake, illnesses that can cause fluid or electrolyte imbalances, and in those using loop diuretics or systemic or inhaled glucocorticoids.
• Ensure serum sodium concentrations are normal before starting or resuming NOCTIVA. Measure serum sodium within 7 days and approximately 1 month after initiating therapy or increasing the dose, and periodically during treatment. More frequently monitor serum sodium in patients 65 years of age and older and in patients at increased risk of hyponatremia.
• If hyponatremia occurs, NOCTIVA may need to be temporarily or permanently discontinued.

INDICATIONS AND USAGE
NOCTIVA is indicated for the treatment of nocturia due to nocturnal polyuria in adults who awaken at least 2 times per night to void.

Nocturnal polyuria was defined in the NOCTIVA clinical trials as nighttime urine production exceeding one-third of the 24-hour urine production.

Before starting NOCTIVA:
• Evaluate the patient for possible causes for the nocturia, including excessive fluid intake prior to bedtime, and optimize the treatment of underlying conditions that may be contributing to the nocturia.
• Confirm the diagnosis of nocturnal polyuria with a 24-hour urine collection, if one has not been obtained previously.

Limitation of Use: NOCTIVA has not been studied in patients less than 50 years of age.

CONTRAINDICATIONS
NOCTIVA is contraindicated in patients with the following conditions due to an increased risk of severe hyponatremia:
• Hyponatremia or a history of hyponatremia [see Warnings and Precautions]
• Polydipsia
• Primary nocturnal enuresis [see Use in Specific Populations]
• Concomitant use with loop diuretics [see Warnings and Precautions]
• Concomitant use with systemic or inhaled glucocorticoids [see Warnings and Precautions, Drug Interactions]
• Renal impairment with an estimated glomerular filtration rate (eGFR) below 50 mL/min/1.73 m2 [see Use in Specific Populations]
• Known or suspected syndrome of inappropriate antidiuretic hormone (SIADH) secretion
• During illnesses that can cause fluid or electrolyte imbalance, such as gastroenteritis, salt-wasting nephropathies, or systemic infection

NOCTIVA is contraindicated in patients with the following conditions because fluid retention increases the risk of worsening the underlying condition:
• Congestive heart failure (New York Heart Association Class II to IV) [see Warnings and Precautions]
• Uncontrolled hypertension

WARNINGS AND PRECAUTIONS
Risk of Hyponatremia: NOCTIVA can cause hyponatremia [see Boxed Warning and Adverse Reactions]. Severe hyponatremia can be life-threatening if it is not promptly diagnosed and treated, leading to seizures, coma, respiratory arrest, or death.

NOCTIVA is contraindicated in patients at increased risk of severe hyponatremia, such as those with excessive fluid intake, those who have illnesses that can cause fluid or electrolyte imbalances, and in those using loop diuretics or systemic or inhaled glucocorticoids [see Boxed Warning, Contraindications, and Drug Interactions].

Before starting or resuming NOCTIVA, ensure that the serum sodium concentration is normal. Consider the 0.83 mcg dose as the starting dose for patients who may be at risk for hyponatremia.

When NOCTIVA is administered, fluid intake in the evening and nighttime hours should be moderated to decrease the risk of hyponatremia. Monitor the serum sodium concentration within 7 days and approximately 1 month of initiating NOCTIVA or increasing the dose, and periodically thereafter. The frequency of serum sodium monitoring should be based on the patient's risk for hyponatremia. For example, more frequent monitoring is recommended for patients 65 years of age or older or those on concomitant medications that can increase the risk of hyponatremia, such as tricyclic antidepressants, selective serotonin reuptake inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), chlorpromazine, carbamazepine, and thiazide diuretics [see Drug Interactions].

If hyponatremia occurs, NOCTIVA may need to be temporarily or permanently discontinued, and treatment for the hyponatremia instituted, depending on the clinical circumstances, including the duration and severity of the hyponatremia.

Fluid Retention: NOCTIVA can cause fluid retention, which can worsen underlying conditions that are susceptible to volume status. Therefore, NOCTIVA is contraindicated in patients with New York Heart Association Class II to IV congestive heart failure or uncontrolled hypertension [see Contraindications]. In addition, NOCTIVA is not recommended in patients at risk for increased intracranial pressure or those with a history of urinary retention, and should be used with caution (e.g., monitoring of volume status) in patients with New York Heart Association Class I congestive heart failure.

Concurrent Nasal Conditions: Discontinue NOCTIVA in patients with concurrent nasal conditions that may increase systemic absorption of NOCTIVA (e.g., atrophy of nasal mucosa, and acute or chronic rhinitis), because the increased absorption may increase the risk of hyponatremia. NOCTIVA can be resumed when these conditions resolve.

ADVERSE REACTIONS
The following adverse reaction is described elsewhere in the labeling:
• Hyponatremia [see Boxed Warning and Warnings and Precautions]

Clinical Trials Experience:

During these trials, serious adverse reactions were reported in 2%, 2%, and 3% of patients with nocturia due to nocturnal polyuria treated with NOCTIVA 0.83 mcg, NOCTIVA 1.66 mcg, and placebo, respectively. There was one case of hyponatremia in the 1.66 mcg group and one case in the placebo group classified as serious adverse reactions.

Adverse Reactions Leading to Discontinuation: Among patients with nocturia due to nocturnal polyuria, the discontinuation rate due to adverse reactions was 4.0% with NOCTIVA 0.83 mcg, 4.4% with NOCTIVA 1.66 mcg, and 2.3% with placebo. Table 1 displays the most common adverse reactions leading to discontinuation in patients with nocturia due to nocturnal polyuria.

Table 1: Most Common Adverse Reactions (≥2 Incidences) Leading to Discontinuation in Patients With Nocturia Due to Nocturnal Polyuria in 2 Double-Blind, Placebo-Controlled Clinical Trials

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>NOCTIVA 1.66 mcg (n=341)</th>
<th>NOCTIVA 0.83 mcg (n=354)</th>
<th>Placebo (n=349)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremia/Blood Sodium Decreased</td>
<td>4 (1.2%)</td>
<td>3 (0.9%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Nasal Discomfort</td>
<td>0 (0.6%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nasal Congestion</td>
<td>2 (0.6%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>2 (0.6%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>2 (0.6%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Dysuria</td>
<td>1 (0.3%)</td>
<td>2 (0.6%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Most Common Adverse Reactions: Table 2 summarizes the most common adverse reactions reported by patients with nocturia due to nocturnal polyuria. This table shows adverse reactions reported in at least 2% of patients treated with NOCTIVA and at a higher incidence with the 1.66 mcg dose than with placebo.
Table 3: Hyponatremia in 2 Double-Blind, Placebo-Controlled Clinical Trials in Patients With Nocturia Due to Nocturnal Polyuria

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>NOCTIVA 1.66 mcg (n=341)</th>
<th>NOCTIVA 0.83 mcg (n=354)</th>
<th>Placebo (n=349)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal Discomfort</td>
<td>20 (5.9%)</td>
<td>12 (3.4%)</td>
<td>17 (4.9%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>13 (3.8%)</td>
<td>8 (2.3%)</td>
<td>10 (2.9%)</td>
</tr>
<tr>
<td>Nasal Congestion</td>
<td>10 (2.9%)</td>
<td>5 (1.4%)</td>
<td>5 (1.4%)</td>
</tr>
<tr>
<td>Sneezing</td>
<td>9 (2.6%)</td>
<td>8 (2.3%)</td>
<td>5 (1.4%)</td>
</tr>
<tr>
<td>Hypertension/Blood Pressure Increased</td>
<td>9 (2.6%)</td>
<td>6 (1.7%)</td>
<td>4 (1.1%)</td>
</tr>
<tr>
<td>Back Pain</td>
<td>8 (2.3%)</td>
<td>4 (1.1%)</td>
<td>3 (0.9%)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>7 (2.1%)</td>
<td>7 (2.0%)</td>
<td>4 (1.1%)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>7 (2.1%)</td>
<td>3 (0.8%)</td>
<td>3 (0.9%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6 (1.8%)</td>
<td>7 (2.0%)</td>
<td>5 (1.4%)</td>
</tr>
</tbody>
</table>

No overall changes were observed in the safety profile during the open-label, uncontrolled extension trial with up to 126 weeks of follow-up.

**Hyponatremia**: Table 3 shows the incidence of serum sodium concentrations below the normal range reported in the 2 placebo-controlled trials.

**Table 3: Hyponatremia in 2, Double-Blind, Placebo-Controlled Clinical Trials in Patients With Nocturia Due to Nocturnal Polyuria**

<table>
<thead>
<tr>
<th>Serum Sodium Concentrations (mmol/L)</th>
<th>NOCTIVA 1.66 mcg (n=341)</th>
<th>NOCTIVA 0.83 mcg (n=354)</th>
<th>Placebo (n=349)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65 years</td>
<td>130-134</td>
<td>42 (12.3%)</td>
<td>33 (9.3%)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>126-129</td>
<td>7 (2.1%)</td>
<td>8 (2.3%)</td>
</tr>
<tr>
<td>&lt;125</td>
<td>5 (1.5%)</td>
<td>0</td>
<td>1 (0.3%)</td>
</tr>
</tbody>
</table>

Of the 5 patients on NOCTIVA 1.66 mcg with serum sodium ≤125 mmol/L, all were 65 years of age or older. Four were men. The onset of the hyponatremia ranged from 6 days to 12 weeks after the start of dosing. Four of these patients were taking a concomitant systemic or inhaled glucocorticoid and 3 were taking an NSAID.

**See**: The incidence of hyponatremia with NOCTIVA was similar in men and women.

**Age**: Patients 65 years of age and older treated with NOCTIVA had a higher incidence of hyponatremia compared to those younger than 65 years of age (see Table 4).

**Table 4: Hyponatremia, Based on Age, in 2 Double-Blind, Placebo-Controlled Clinical Trials in Patients With Nocturia Due to Nocturnal Polyuria**

<table>
<thead>
<tr>
<th>Serum Sodium Concentrations (mmol/L)</th>
<th>NOCTIVA 1.66 mcg &lt;65 years (n=146)</th>
<th>NOCTIVA 1.66 mcg ≥65 years (n=199)</th>
<th>NOCTIVA 0.83 mcg &lt;65 years (n=148)</th>
<th>NOCTIVA 0.83 mcg ≥65 years (n=206)</th>
<th>Placebo &lt;65 years (n=144)</th>
<th>Placebo ≥65 years (n=205)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65 years</td>
<td>130-134</td>
<td>14 (9.6%)</td>
<td>28 (14.4%)</td>
<td>8 (5.4%)</td>
<td>25 (12.1%)</td>
<td>7 (4.9%)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>126-129</td>
<td>7 (3.6%)</td>
<td>2 (1.4%)</td>
<td>6 (2.9%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≤125</td>
<td>0</td>
<td>5 (2.6%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (0.5%)</td>
</tr>
</tbody>
</table>

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**: There are no data with NOCTIVA use in pregnant women to inform any drug-associated risks. No adverse developmental outcomes were observed in animal reproduction studies with administration of desmopressin during organogenesis to pregnant rats and rabbits at doses approximately <1 and 31 times, respectively, the maximum recommended human dose based on nasal surface area (see Data).

NOCTIVA is not recommended for the treatment of nocturia in pregnant women. Nocturia is usually related to normal physiologic changes during pregnancy that do not require treatment with NOCTIVA.

In the U.S. general population, the estimated background rate of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

**Data**

**Animal Data**: Desmopressin acetate did not cause fetal harm in teratology studies in rats and rabbits at doses of 0.05 to 10 mcg/kg/day, which is approximately <1 times (rat) and 31 times (rabbit) the maximum recommended human dose based on nasal surface area.

**Lactation**: Desmopressin is present in small amounts in human milk and is poorly absorbed orally by an infant. There is no information on the effects of desmopressin on the breastfed infant or on milk production. The development and health benefits of breastfeeding should be considered alongside with the mother’s clinical need for NOCTIVA and any potential adverse effects on the breastfed infant from NOCTIVA or from the underlying maternal condition.

**Pediatric Use**: NOCTIVA is contraindicated for the treatment of primary nocturnal enuresis because of reports of hyponatremic-related seizures in pediatric patients treated with other intranasal formulations of desmopressin. Studies of NOCTIVA have not been conducted in pediatric patients [see Contraindications].

**Geriatric Use**: Patients 65 years and older treated with NOCTIVA had a higher incidence of hyponatremia compared to patients less than 65 years old treated with NOCTIVA [see Warnings and Precautions, and Adverse Reactions].

**Renal Impairment**: Desmopressin is mainly excreted in the urine. The area under the concentration-time curve (AUC) and terminal half-life of desmopressin in renally impaired patients with an eGFR below 50 mL/min/1.73 m2 is 3- to 4-fold greater than in patients with an eGFR above 50 mL/min/1.73 m2. Therefore, NOCTIVA is contraindicated in patients who have renal impairment with an eGFR below 50 mL/min/1.73 m2 [see Contraindications].

**Hepatic Impairment**: The effect of hepatic impairment on the pharmacokinetics of desmopressin has not been studied.

**OVERDOSE**

Signs of overdose may include effects from hyponatremia such as seizure, altered mental status, cardiac arrhythmias, and worsening edema. Other signs of overdose may include oliguria and rapid weight gain due to fluid retention [see Warnings and Precautions]. In case of overdose, NOCTIVA should be discontinued immediately, serum sodium should be assessed, and appropriate medical treatment initiated.

**PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

**Hyponatremia**: Inform patients that NOCTIVA can cause hyponatremia, which may be life-threatening. Inform patients to moderate fluid intake in the evening and nighttime hours, to monitor for symptoms of hyponatremia (such as headache, nausea or vomiting, restlessness, fatigue, drowsiness, dizziness, muscle cramping, or altered mental status), to undergo recommended serum sodium measurements, to inform their health care provider about new medications, and to stop NOCTIVA during illnesses that can cause fluid or electrolyte imbalance [see Boxed Warning, Dosage and Administration, Contraindications, and Warnings and Precautions].

**Nasal Conditions**: Inform patients to discontinue NOCTIVA if nasal conditions occur that may interfere with the absorption of NOCTIVA [see Boxed Warning, Dosage and Administration, Contraindications, and Warnings and Precautions].

**Pregnancy**: Inform patients that NOCTIVA can cause hyponatremia, which may be life-threatening. Inform patients to moderate fluid intake in the evening and nighttime hours, to monitor for symptoms of hyponatremia (such as headache, nausea or vomiting, restlessness, fatigue, drowsiness, dizziness, muscle cramping, or altered mental status), to undergo recommended serum sodium measurements, to inform their health care provider about new medications, and to stop NOCTIVA during illnesses that can cause fluid or electrolyte imbalance [see Boxed Warning, Dosage and Administration, Contraindications, and Warnings and Precautions].

**Nasal Conditions**: Inform patients to discontinue NOCTIVA if nasal conditions occur that may interfere with the absorption of NOCTIVA [see Boxed Warning, Dosage and Administration, Contraindications, and Warnings and Precautions].

**Lactation**: No adverse effects on breastfeeding have been reported. Lactation: [see Warnings and Precautions].

**Manufactured for**: Avadel Specialty Pharmaceuticals, LLC

Chesterfield, MO 63005

Rev 03/2018 [Ref 12/2017]

PM-US-NTV-0164-0.4
What are your options?

401(k) with a previous employer: What are your options?

Several strategies are available, each with their own pros and cons.

**Q:** I have an old 401(k) account with a former employer. Should I leave it there for as long as they’ll let me? If not, what are my options?

**A:** Generally, you have four options when it comes to your old employer-sponsored retirement plan. You may be able to leave it with the old employer, you can roll it into your new employer’s retirement plan (if eligible), you can roll the money into an Individual Retirement Account (IRA) rollover account, or you can take a cash distribution. Each of these alternatives has advantages and disadvantages.

For many individuals, taking a cash distribution is the least desirable option since any distributed amount not rolled into a new plan will be subject to income taxes and a 10% penalty if you are under age 59½. The taxable portion will be counted as ordinary income during the year of distribution and could result in moving you into a higher tax bracket. Due to the severity of the taxes and penalty, cash distributions should only be considered in cases of true financial hardship such as foreclosure, eviction, or repossession.

If the plan permits, leaving the retirement account with your former employer has some advantages, such as familiar investment options and possibly lower fees. Additionally, if it is a qualified retirement plan, it may offer protection from malpractice lawsuits and other creditors. Before making the asset protection feature a deciding factor, check if your new employer plan offers the same protections. Many of them do.

**Retirement assets left with previous employers can be forgotten (yes, it happens!), or the previous employer may change names or be acquired down the road.**

It may make more sense, however, to roll the funds into the qualified retirement plan provided by your new employer or into an IRA rollover. Retirement assets left with previous employers can be forgotten (yes, it happens!), or the previous employer may change names or be acquired down the road. This can make tracking down these old plans very difficult and time consuming. Therefore, consolidating your retirement accounts through a rollover may be the better option. It simplifies the management of your retirement savings by combining multiple accounts into just one or two.

When deciding whether to roll your account(s) into your new employer’s plan or an IRA, it is important to examine the differences between the two vehicles. Both will maintain the tax benefits of the previous account, and no taxes or penalties are incurred by moving the funds. The biggest difference between the two account types is the available investment options. Your new employer’s plan may only offer a limited selection of investment options. The number of funds could range from less than 10 investment options to dozens. These funds may have a history of strong performance with low fees or they could not.

It is important to review the options before committing to rolling the funds into that plan. An IRA rollover, on the other hand, allows you to invest in any publicly traded security. You may be able to find better-performing funds that have lower internal expense ratios.

Another difference between the two rollover options is the cost. When using your employer’s retirement plan, the cost may be assumed by the employer. This includes paying a record keeper, a third-party administrator, and often an investment adviser. The employee just needs to pay the internal expense ratio of the funds themselves. With an IRA rollover, the responsibility of paying an investment adviser may fall to the individual investor.

If an individual does not have extensive experience selecting funds and designing an investment allocation, working with an adviser is recommended. Most advisers charge a fee for their services and that should be factored into the decision.

Due to the complexity of each option and the consequences involved, we recommend speaking with a financial adviser to determine the best option for you.

**Q:** We have finally scheduled an appointment with our attorney to prepare an estate plan. What should we do in preparation for the meeting?

**A:** Estate planning can range from simple and straightforward to sophisticated and complex. The starting point, prior to meeting with the attorney, would be to prepare a complete list of assets, including investments, retirement accounts, insurance policies, real estate, and any business/practice interests. Next, decide what you want to do with those assets: who should inherit them, who should manage your estate, and who should make significant decisions if you become incapacitated. This will provide a nice framework for the attorney to begin the process.

FINANCIAL TIPS

- The four options for handling an old employer-sponsored 401(k) are: leave it with the old employer, roll it into the new employer’s retirement plan (if eligible), roll the money into an IRA rollover account, or take a cash distribution.
- Consolidating retirement accounts through a rollover simplifies the management of retirement savings by combining multiple accounts into just one or two.
- Prior to meeting with an estate-planning attorney, a good starting point is to prepare a complete list of assets, including investments, retirement accounts, insurance policies, real estate, and any business/practice interests.
Hiring a coder: How to recruit and retain the right candidate

Follow these tips in order to land the ideal hire for your practice

Morgan recommends practice leaders—which can include the practice manager or administrator, the practice owners, and the manager of the billing team—meet to align on what the coding job will entail and develop a comprehensive job description.

“[Practices] are not giving enough weight to certifications... If they’re certified, you know they’ve passed an exam showing competency.”

— RAEMARIE JIMENEZ, CPC
VICE PRESIDENT OF MEMBERSHIP AND CERTIFICATION SOLUTIONS, AAPC

“[They must decide] if this person is working only on coding or on billing as well,” she said.

A coder by trade, Astara Crews, CHC, CPC, director of regulatory affairs at ENT & Allergy Associates LLP, a group practice with offices in New Jersey and New York, says that the coder’s role often depends on a practice’s size and revenue because smaller practices tend to not have the business need and/or resources to support distinct coding and billing roles.

But having a joint biller and coder role can be valuable to a practice.

“Having [a biller] who is aware of the coding rules adds that extra layer of assurance that [claims] are not going out fraudulently,” Crews said.

Describe your ideal candidate

In order to screen the best candidates, identify the qualifications and experience a coder must have to be successful in the coding position in addition to the soft skills needed to work effectively with other staff members.

Jimenez recommends limiting your scope to candidates with professional certification.

“[Practices] are not giving enough weight to certifications. They will hire someone just to sit in that seat, thinking that [coding] is an easy job, and they don’t get well-trained individuals. If they’re certified, you know they’ve passed an exam showing competency.”

Keep in mind that individuals could have a compelling case for why they would excel in the position, even if their backgrounds do not exactly match the job requirements, Morgan says.

For example, do not discount candidates simply because their certifications are not specific to your practice’s setting or specialty.

“If the candidate learned how to do coding successfully for several different specialties in the past, then that may be an indication that they will be very adept at learning a new specialty,” she said.

Furthermore, coders who are new to the industry can become valuable assets if training and supervision are available.

“I used to work with coding externs who were completing a course and getting certified,” Jimenez said. “For me, it was beneficial [to host them] because they came with no bad habits, so I was able to teach them the way I wanted it done in our particular circumstance.”

Create a compelling job ad

Pique applicants’ interest by posting a job ad that not only includes key information about the job but also demonstrates why applicants should want to work at your practice.

Posting the job description alone will not be alluring to applicants because it will be too bureaucratic, Morgan says.

“You need to convey your practice’s personality, history, and mission. Why is your practice an exciting place to work? Is your practice a dynamic place to work? A compassionate place to work?”

Also consider how digestible your job ad will be for a reader, Morgan says. For example, avoid large blocks of text and the use of obscure or vague terms to describe the job duties. Use bullet points, shorter phrases, and clear language.

Recruit from the right places

Engage in both active and passive recruitment to generate a strong candidate pool.

To reach candidates actively searching for a
Medicai malpractice insurance is one of the greatest expenses physicians face during their careers. But knowing what to look for in a policy is a mystery for many physicians, as well as a time-consuming chore that rarely gets the attention it deserves. And buying the wrong type or incorrect amount of insurance—or buying it from the wrong carrier—can be extremely costly. Physicians who take the time to understand how to buy malpractice insurance will not only save money, but ensure that they’ve got the right type and amount of liability coverage.

Types of insurance

Policies typically cover expenses incurred while defending and settling malpractice suits. These can include attorney fees, medical damages, arbitration and settlement costs, court costs, and punitive and compensatory damages. Liabilities incurred from criminal acts or sexual misconduct usually are not covered.

There are two basic types of malpractice insurance: claims-made and occurrence. A claims-made policy provides coverage only if the policy is in effect both when the incident took place and when a lawsuit is filed. Occurrence policies cover any claim for an event that took place during the

JAMES F. SWEENEY
Mr. Sweeney is a contributor to Urology Times sister brand Medical Economics, where this article was originally published.

As a coder, the primary function is not only to code a service but also to interact with [the team] as part of education," Crews said, noting that a coder needs have interpersonal skills and be adaptable to change. As a competitive salary typically is the main draw to an open position, consider setting the salary for your coding position in line with what other practices provide.

The AAPC salary survey calculator is a useful resource for practices that want to judge if their compensation offerings are competitive, Jimenez says (bit.ly/AAPCsalarycalculator). The calculator allows employers to search the average state salary by certification, education level, and health care work experience.

But if your practice cannot afford to match what other practices pay, additional benefits such as a 401(k), vacation days, and sick leave can make your position more attractive. Coding also lends itself to remote work, which Jimenez says “can be a significant financial saver for the individual and employer” as well as offer the individual more flexibility and work-life balance.

Crews suggests providing career growth opportunities and support to attract candidates. Think about covering the cost of the coder’s continuing education units that are required to maintain certifications, membership dues to professional organizations, or providing financial support and time off to attend professional conferences, she says.

“Once competitive, I think a practice should look at the individual as not just a body to fill a seat or a body to fill a coding position… but look at the individual as a whole and try to recruit individuals based on what they have to offer,” Crews said, stressing that “not-so-great salary” can be offset with opportunities for professional growth and development to successfully attract coding talent.

Medical Economics is a sister brand to Urology Times, where this article was originally published.

Please see INSURANCE, page 41
INSURANCE
continued from page 40

period the policy was in effect, even if the claim is filed after the policy lapses.

Because a claim can be filed years after an event and after a claims-made policy expires, these policies often include a “tail” that extends coverage for a set number of years beyond the expiration date. If it’s not part of the original policy, tail coverage can be bought separately.

Tail coverage offers protection when a physician is changing jobs or carriers or retiring. Sometimes, the cost of tail coverage will be covered by a previous employer to protect itself or can be negotiated with a new employer. Occurrence policies generally don’t require tail coverage, but are not available in all states.

If buying a claims-made policy, be sure that the beginning date for coverage is accurate and matches the date on the prior policy to ensure there are no coverage gaps between policies, says Jennifer Richard, ARM, RPLU, vice president of sales and marketing, Professional Risk Associates, a Virginia-based malpractice insurance broker.

“Physicians should ensure all services they are providing have been fully disclosed and reviewed by their agent and underwriter to ensure there are no gaps in coverage in their practice,” she said.

“Additionally, it’s important they review all other professional liability exposures within cyber, regulatory, directors and officers, and employment practices liability. There are situations where these coverages could overlap, or come into play, based on the risk exposure of the practice.”

How much coverage?
The appropriate amount of coverage can vary by state, specialty, and contractual arrangements with hospitals and other health care organizations, says Richard. Some states require providers have minimum levels of coverage, but a physician can still need more.

In general, carriers’ standard coverage limits are $1 million per claim and $3 million aggregate, which is the most the policy will pay in a year for all claims. However, certain states require different limits based on medical malpractice caps on damages. States with more litigious climates might require more.

Richard cites the example of Virginia, which does not have a statutory requirement for medical liability insurance. However, the state has a medical malpractice cap of $2.35 million (which eventually will increase to $3 million). For that reason, hospitals require physicians to carry at least that amount with an aggregate that is three times higher ($7.05 million per claim/$2.35 million aggregate).

Some states have patient compensation or catastrophe loss funds, which provide an additional layer of coverage over the primary policy limits, says Eric Anderson, vice president of marketing and communications for Medical Professional Liability Associates, an industry group.

Providers pay into these state-run funds through a surcharge on medical malpractice insurance premiums. If a lawsuit is filed and found to be legitimate, malpractice insurance will cover the injured patient’s costs to a limit set by the state. The rest is paid by the fund.

What to look for in a carrier
Carriers must be licensed in each state in which they operate and follow that state’s rules and regulations. While many carriers operate in multiple states, not all do. Patrick Lawn, owner of Physicians Insurance Consultants in Pennsylvania, estimates that there is an average of five to six carriers in each state.

“Physicians should ensure all services they are providing have been fully disclosed and reviewed by their agent and underwriter to ensure there are no gaps in coverage in their practice.”

JENNIFER RICHARD, ARM, RPLU
VICE PRESIDENT OF SALES AND MARKETING,
PROFESSIONAL RISK ASSOCIATES

Price is an important factor, but it shouldn’t be the only one, says Lawn, adding that shopping on price alone can lead to hiring an unreliable or financially precarious carrier.

“You can’t just jump (carriers) for a penny; you’ve got to be able to rely on the carrier,” Lawn said.

Make sure the policy has a consent to settle clause, which prevents the insurer from settling a claim without permission of the insured doctor, Lawn advises.

The best carriers will act as resources for their clients, offering advice on how to avoid claims and other matters, says Kenneth Hertz, FACMPE, principal consultant at Medical Group Management Association (MGMA).

“Partner with them as a resource. They’re the experts. They’re only too happy to help and they can help you stay out of trouble. It’s to their benefit as well,” he said.

He recommends screening potential carriers on a variety of criteria, in addition to price:

• Ask medical colleagues and people in the insurance industry about the carrier’s reputation. How responsive is it? What’s its history on settling claims?

• Check the carrier’s financial security on A.M. Best, which reports on the financial stability of insurers and rates individual companies. Look for a carrier with an “A,” Excellent rating or better and a “Stable” outlook.

• How long has the carrier been in business? Does it specialize in certain fields, such as obstetrics?

• Does the carrier have a local office or counsel? Is it willing to visit the practice and become familiar with the caregivers?

Should you use a broker?
Virginia Kladder, MD, considers herself fortunate that she’s never had to shop for malpractice insurance.

“If I had to go out on my own there is no way, as a physician, I could figure it out,” she said.

The Richmond, VA internist works for PartnerMD, a concierge practice. Buying insurance for Dr. Kladder and 23 other physicians across eight offices in five states is the responsibility of PartnerMD’s Chief Operating Officer Jack Bretcher, who, in turn, relies on insurance broker Professional Risk Associates.

A broker has the depth of knowledge and the experience to know the coverage a practice needs and the best insurers to provide it, Bretcher says.

“They help us keep abreast of what’s out there and what our needs are,” he said, adding that he’s bought extra layers of coverage, including cyber insurance, at the recommendation of his broker.

Even small practices are better off using independent brokers rather than spending the time to research policies and carriers, says MGMA’s Hertz, a former practice manager.

“If you can find a broker who is knowledgeable, it’s a lot easier to hire them to do the legwork, get the quotes, and educate you as a manager,” he said.

Risk retention groups
An alternative to traditional malpractice insurance is a risk retention group (RRG). These are liability insurance companies that require all company owners to be policyholders and vice versa.

All owners/policyholders must be in the same type of business, such as physicians. RRGs can offer lower premiums than traditional carriers and, if they are profitable, the owners are paid dividends, but there are drawbacks as well, says Hertz. They must be incorporated in at least one state.
Three low-tech ways to boost collections in your practice

AVERY HURT
Ms. Hurt is a contributor to Urology Times sister brand Physicians Practice, where this article was originally published.

If you’re looking for new ideas to improve your billing and collections, don’t exclusively focus on technology. We usually don’t think of low-tech solutions as innovative, but some of the best changes you can make don’t involve software. Here are three old-fashioned ways to help you get the job done.

Keep it simple. Everyone wants to be able to make sense of their medical bills, regardless of how they are delivered. “Medical bills can be confusing, even daunting,” said Brennan Cantrell, commercial health insurance strategist for the American Academy of Family Physicians (AAFP). Bills don’t have to be overwhelming, though.

A little tweaking can make them easy to understand. The best way to update your invoices is to strip them down to the basics: balance, date of service, due date, and a number to call with questions. “If the bill is too hard to understand, the patient is more likely to put it aside to deal with later,” Cantrell said. By putting only the necessary information on the bill, you make it easier for patients to pay—and that means they’re more likely to pay promptly.

Learn the magic words. Asking for money is not everyone’s strong suit. Be sure your staff is well trained in the best collection practices. This means knowing how to stay on the right side of collections law as well as how to communicate effectively. Barbie Hays, CPC, coding and compliance strategist for the AAFP, suggests having scripts for employees to follow. “It’s important to teach them not only what to say, but what not to say,” she said.

Training shouldn’t be limited to the front desk. Back office staff need to know the basic fee schedule, too. Nurses and physicians are often asked about costs and payment arrangements. Sometimes, a provider may reassure a patient who is worried about the cost of a procedure without really knowing what the procedure costs. Back office staff also need to know how to talk about payments legally and know not to promise patients things the billing office can’t deliver.

Skip the robocalls. Automated reminders can save time, but they might cost a practice in other ways. It may be beneficial to have someone from the office call with appointment reminders. When a human being calls, he or she can say something like, “I just wanted to remind you of your appointment Thursday. Be sure to bring your insurance information and copay when you come.”

Hays acknowledges that a recording could communicate the same message, but it probably won’t have the same effect. It’s far easier to ignore a reminder from a recording than from a friendly person who you might know or see in the next few days. Plus, a live call is a chance for patients to ask any questions in advance to make sure prior authorizations are completed and information is up to date.

Technology has made billings and collections easier. However, there are times when it’s best to stick to old-fashioned methods. Investing in a person may improve staff efficiencies and improve patient experiences.

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one state but can operate nationwide, largely exempt from the oversight of other state insurance departments.

Because they were created by federal law, they are not subject to the same level of state regulation as private carriers. They may not have to disclose as much financial information and they are not backed by state guaranty funds in case of financial troubles.

Practices should perform due diligence on RRGs before deciding to join one, Hertz says. Sources of information about them are Demotech and Risk Retention Reporter.

Shopping and updating

Shopping for malpractice insurance can be a time-consuming task, so it’s not surprising that physicians tend to stick with a carrier and policy unless something changes, such as a large increase in premiums or a contentious claim. That complacency can be costly, says Lawn.

“I’ve seen doctors who are looking to save expenses, but they don’t bother [comparison] shopping one of their highest overhead expenses. It makes no sense to me,” Lawn said.

But that doesn’t mean shopping every year, says Richard, who adds that practices should review their policies and compare prices every 2 to 3 years.

Ask carriers about ways to earn discounts, says Hertz, who adds that some insurers will offer discounts of up to 10%-15% if doctors attend carrier-led risk management programs on how to avoid malpractice claims through such things as documentation and better patient communication.

Even if not shopping for a new carrier, physicians should periodically check if their coverage needs updating to account for developments since the policy was purchased. Richard says the following can result in a need for policy changes:

• adding a provider
• starting a joint venture or new business
• forming a new entity
• changing employers
• any changes in practice parameters, such as new services or using new equipment.

“If you have any questions at all, you should reach out to your agent, as they can guide you through practice exposure changes,” she said.
Shared decision-making presents opportunity for APPs

BPH management, active surveillance lend themselves to APP involvement

ADELE M. CARUSO, DNP, CRNP

Dr. Caruso is a nurse practitioner at the University of Pennsylvania Health System, Philadelphia.

Implementing a shared decision-making model

The decision-making process often occurs in the absence of any framework to guide patients. Studies suggest that although providers identify shared
decision-making as their preferred style of decision-making over paternalism (BMC Fam Pract 2007; 8:10), fewer than 10% utilize shared decision-making effectively (Cochrane Database Syst Rev 2003; CD001431). Elwyn et al propose a three-step process for incorporating a shared decision-making model into clinical practice (J Gen Intern Med 2012; 27:1361-7). This includes: choice talk, option talk, and decision talk, where the provider supports deliberation throughout the process.

Choice talk refers to making sure that patients know that reasonable options are available. Option talk refers to providing a structured conversation with detailed information about the treatment options with the risks and benefits of treatment outcomes, and decision talk refers to the process of considering preferences—being respectful and responsive based on their risk-benefit profile, their personal utility values (ie, either cure focus or quality of life focus), competing comorbidities, and deciding what is best.

Finding a decision aid

In a busy practice, decision aids can facilitate the process of shared decision-making. These tools assist patients in participating in the decision-making process and provide them information regarding their treatment options. Decision aids help patients clarify and communicate the utility values they associate with different features of the treatment options, as well as illuminate their preferences (bit.ly/QIsummitpaper).

When information is presented in a graphic or “theatric” form, patients may more quickly grasp the key aspects of their medical situation. A good decision aid describes the health condition and the benefits and harms of each option in balanced detail. Review for content (not too complex) and for accuracy. Incorporate into your clinical practice, especially for conditions you encounter regularly.

APPs can manage a variety of urologic conditions that often require extensive counseling and can do so with relative autonomy.

APPs can manage a variety of urologic conditions that often require extensive counseling and can do so with relative autonomy. This may be a component of their independent practice or in collaboration with their physician colleagues. For instance, examples include conditions such as an elevated PSA or BPH management, patients who require active surveillance for prostate cancer, or the emerging population of patients with small renal masses. Additionally, this APP contribution to urologic practice allows for increased productivity by enabling the urologic surgeon to perform other tasks and the ability for the APP to offer a wider array of services.

Consider creating and implementing a shared decision-making model of your own. Consider decision aids as part of that model, as many can be incorporated seamlessly and efficiently into the patient encounter.

I say, advocate for an individualized approach and make shared decision-making a reality in your clinical practice!

As always, please feel free to share your perspective by emailing me at UT@advanstar.com.
Are your in-office clinical lab services profitable?

Payments have been reduced for many lab tests

M any urology practices currently operate in-office clinical labs that have proven profitable while also providing one-stop shopping for their patients. Since urologists serve so many Medicare beneficiaries, the effects of recent major changes in the method that Medicare reimburses these labs make it critical that the business management team evaluate the revenue and costs of clinical lab services annually to determine if this service remains financially viable.

In 2016, the Centers for Medicare & Medicaid Services (CMS) issued proposed new rules that base Medicare clinical lab fee schedule (CLFS) reimbursements on comparison data compiled from mandatory reporting from independent labs, physician office labs, and urgent care centers. The complexity of the information reporting structure resulted in the postponement of changes in the CLFS until Jan. 1, 2018.

Payments reduced for approximately 75% of tests

An analysis of the 2018 CLFS published by the American Medical Association in October 2017 showed that the payments were reduced for approximately 75% of lab tests (bit.ly/CLFSanalysis). Fee cuts for each clinical laboratory testing code were limited to 10% per year from 2018 through 2020. Additional reporting data would be analyzed annually to compare physician office lab fees with the potential for a 15% cut per year from 2021 through 2023.

For a typical urology office-based lab, the resulting Medicare fee cuts from 2017 to 2018 are as follows:
- Urinalysis CPT Code 81000: from $4.35 in 2017 to $4.02 for 2018—minus 7.6%
- PSA CPT Code 84153: from $25.23 in 2017 to $22.71 for 2018—minus 10%
- Urine culture CPT Code 87086: from $11.07 in 2017 to $9.96 for 2018—minus 10%

Labs with higher complexity Clinical Laboratory Improvement Amendments classifications deliver a greater variety of tests, and many have higher fees for them. The net revenue reduction should be evaluated annually. In addition, the increasing costs of lab supplies, equipment services costs, quality testing services, and staff compensation must be reviewed. As the profit margin shrinks from year to year, a savvy urology practice must make strategic decisions about whether to divest its lab operations to an outside manager or consider it to be a “loss-leader” to preserve those patient services that may differentiate it from its competition.

According to an article by Jeremy Belanger of the Chapman Law Group about these changes, a revision in the threshold that determines which labs are required to report their fees to CMS may even increase the administrative expenses further for office-based labs in 2019 (bit.ly/labfeechanges). The proposed Medicare fee schedule rule published in July by CMS included requests for comments on changing the low expenditure threshold for reporting. Comments were requested on lowering it to $6,250, which would pull in more small labs, or raising it to $18,750, which could do the opposite. Belanger explains that this could result in an “increased burden on practitioners to collect and report data.”

The reporting costs will be an important factor in the profitability analysis moving forward.
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the epidemic under control,” said Dr. McGovern, who has presented on
the issue of opioid prescribing at AUA annual meetings.

Overprescribing is real
Urologists commonly overprescribed postoperative narcotics after urologic surgery, researchers reported in the Journal of Urology (2011; 185:551–5). Sixty-seven percent of patients who had undergone urologic surgery at the University of Utah had leftover opioids, including hydrocodone and oxycodone, after their initial prescriptions. More than 90% received no instructions for how to safely dispose of unused meds, the study authors found.

In the recent Urology study, Dr. Davies and colleagues examined opioid prescription use in 155 opioid-naïve patients who had robotic prostatectomy, robotic partial nephrectomy, open prostatectomy, or open partial nephrectomy from January 2017 to May 2017. Researchers surveyed patients 3 to 4 weeks postoperatively asking how many of the prescribed drugs were used.

They found opioid prescribing far exceeded use from 1.9- to 6.8-fold for the procedures studied.

“Overall, a total of 4,065 oxycodone-equivalents were prescribed during this study and 60% of pills prescribed went unused. This resulted in 2,622 excess pills in the community,” the authors wrote.

Dr. Davies said even he was shocked at patients’ low usage of narcotics following robotic nephrectomy and prostatectomy.

“We averaged eight pills. And when you actually talk to patients, many people took none. Even among the ones that did take a good amount, many said they didn’t need to but they took them because they had the pills,” Dr. Davies said.

There is great variation in opioid prescribing patterns among urologists, according to Greg Auffenberg, MD, MS, who conducted research on opioid prescribing in urology while at the University of Michigan. Today, he’s assistant professor of urology at Northwestern University, Chicago.

“Research out of Dartmouth recently showed among patients taking no opioids before surgery, somewhere between 5% and 7% were still taking opioids 3 to 6 months after surgery, which is beyond when they should still have surgical pain,” Dr. Auffenberg said.

Solutions to a crisis
Mass General Hospital is attacking opioid over-prescribing with clinical pathways that focus on use of alternative pain management options, multidisciplinary collaboration, and patient education, according to Dr. McGovern.

Preoperatively, surgeons can use non-narcotic medications, such as celecoxib (Celebrex), which has been shown to lower patients’ postoperative need for opioids, Dr. McGovern said.

“Urologists should collaborate with anesthesia colleagues to utilize nonopioid alternatives for pain management during and after surgery when possible. Utilization of blocks, including...

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regional or local anesthetics, can greatly reduce surgical patients’ narcotic needs, he said. “For example, patients having major intra-abdominal surgery, such as operating on a large kidney tumor with major debulking of lymph nodes or possible invasion of the vena cava; these patients would be best served by placement of an epidural or regional anesthesia in addition to general anesthesia that they will receive intraoperatively,” Dr. McGovern said. “Postoperatively, the epidural can be utilized to give them a regional block.”

Mass General surgeons first try local blocks, including incisional blocking, which Dr. McGovern said are extremely helpful in reducing the postoperative opioid use. Decreasing opioid use during and immediately after surgery offers many potential benefits, including decreased risk of readmission, according to Dr. McGovern. He said a soon-to-be-published study by Massachusetts General researchers found the number of opioids consumed even in the first 24 hours perioperatively can predict whether a patient will likely be readmitted to the hospital. In essence, high opioid use is linked with more likely hospital readmission.

“In the United States, the most common reason for a postoperative surgical patient from all types of surgery to re-present to an emergency room is with the chief complaint of nausea and vomiting,” Dr. McGovern said. “Opioid-related adverse events include respiratory suppression, nausea, vomiting, urinary retention, difficulty voiding, cognitive impairment, constipation. In rare cases, respiratory suppression can be severe enough that it leads to death from respiratory arrest.”

There are still other reasons urologists and other clinicians should think twice about prescribing opioids. One is that taking high doses of opioids intraoperatively and immediately postoperatively can create a hyperalgesia-like syndrome where patients even weeks later are more sensitive to pain, according to Dr. McGovern.

Like Dr. Davies, Dr. McGovern studied his own approach to surgery to optimize outcomes and potentially lower opioid prescribing. “I have now done over 4,000 radical prostatectomies,” Dr. McGovern said. “In the first 2,000, we gave patients a [patient-controlled analgesia] or low-dose continuous morphine pump. Those patients had much longer hospitalization and greater readmission rates. Now with preemptive Tylenol and Celebrex and giving a rectus sheath block, numbing the rectus abdominis, patients go home on post-op day one. The readmission rate is under 1%. Complication rates are also considerably reduced.”

Dr. McGovern lets patients know he’ll prescribe some opioids to manage acute, significant pain if the patient absolutely needs them. But, he said, by the time he educates patients about what to expect and the potential consequences of opioid use, many become partners in the goal to go without.

He and colleagues make it a point to educate floor staff, nursing, nurse practitioners, and physician assistants about the goal to reduce opioid use.

“We have significantly reduced our need for opioids post-op,” Dr. McGovern said. “The amount that we’re sending patients home with now is down to about 25% of the number of pills that we used to send patients home with.”

At Stanford Health Care in Stanford, CA, a similar strategy has led to a 46% decrease in opioid use in patients who underwent a range of urologic cancer surgeries without increasing their pain or anxiety, researchers reported last month at the American Society of Clinical Oncology’s Quality Care Symposium in Phoenix. The group’s two-pronged approach involves care pathways for post-op pain control using non-opioid medications as first-line therapies and a change in postoperative patient conversations in which nurses, rather than routinely asking patients if they want opioids, discuss current non-opioid medications patients are receiving for pain and ask whether those medications are sufficient.

“With the new approach, opioids were never

“With this, we have significantly reduced our need for opioids post-op,” Dr. McGovern said. “The amount that we’re sending patients home with now is down to about 25% of the number of pills that we used to send patients home with.”

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“With the new approach, opioids were never
withheld, but they were no longer the automatic default for patients and providers,” said lead author Kerri Stevenson, MN, NP-C, a nurse practitioner at Stanford.

**No to narcotics**

Dr. Davies said that none of his robotic surgery patients had received narcotics in the 6 weeks prior to his September 2018 interview with *Urology Times*. In the past, he’d write prescriptions for an average 25 opioid pills for patients about to undergo partial nephrectomy or robotic prostatectomy, he said.

“I haven’t gotten a single patient complaint. And I don’t think I’m going to,” Dr. Davies said. “As long as my patients are preoperatively warned, they’re told to manage their expectations correctly, and as long as their pain is treated correctly, the patients will be fine. Patients can be treated with Motrin and Tylenol just fine. They don’t need narcotics.”

Dr. McGovern said he enjoys practice more because his patient outcomes are better with less opioid use. They recover faster and their recovery is safer, and they’re less likely to call the office at night and on weekends during the perioperative recovery, he said.

“Since doing these blocks, I have not needed to refill anyone’s pain medicine after their first discharge prescription from the hospital,” Dr. McGovern said. “So, I would caution all urologic surgeons to be very careful of refilling opioid pain prescriptions postoperatively after one week or so of surgery. If they do need to refill, then they should consider referring patients to a pain clinic where pain specialists evaluate patients for nonopioid solutions to their pain.”

Opioids might be an appropriate drug for cancer pain but not for acute post-surgical pain, but they’re not worth the consequence of potential addiction in surgical and other urologic patients, according to Dr. Davies, whose best friend died of a heroin overdose in 1999, when Dr. Davies was a fourth-year medical resident. He wrote about the experience in the article, “I lost my best friend to opioids. Yet, as a surgeon I overprescribed them,” published earlier this year in Forbes.

“I do about 400 or 500 major cases a year,” Dr. Davies said. “Can you imagine how many cases in my lifetime I’ve addicted? It’s a pretty stark reality. I have no intention of doing that any further.”

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**Learn more at AUA opioid stewardship summit**

Urologists who want to learn more about opioid stewardship should consider attending the AUA 2018 Quality Improvement Summit at AUA headquarters in Linthicum, MD, Saturday, Dec. 8, 2018. They can sign up for the event focusing on opioid stewardship in the specialty at bit.ly/Opioid-summit.

Greg Auffenberg, MD, MS, the summit’s co-chair, said the day-long event will feature about a dozen speakers from multiple disciplines, including surgical fields, pain medicine, addiction medicine, complementary alternative medicine, and public policy.

“We’re encouraging urologists to attend,” Dr. Auffenberg said. “It’s designed to be an interactive conference where people come and share their perspectives.”

The AUA will post video content from the summit in the weeks following the event and plans and plans to disseminate educational content for urologists and patients from the meeting, he said.
**Breakthrough designation granted for metastatic CRPC agent**

The FDA has granted Breakthrough Therapy designation for rucaparib (Rubraca) as a monotherapy treatment of adult patients with BRCA1/2-mutated metastatic castration-resistant prostate cancer who have received at least one prior androgen receptor-directed therapy and taxane-based chemotherapy. The designation was based on initial efficacy and safety results from TRITON2, the phase II study of rucaparib in men with advanced prostate cancer with BRCA1/2 mutations (germline or somatic) and deleterious mutations of other homologous recombination repair genes, in the metastatic castration-resistant setting. Developer Clovis Oncology, Inc. said initial data from the TRITON2 clinical study will be presented for the first time at the European Society for Medical Oncology annual congress in Munich, Germany.

**Drug combo shows positive phase III results in advanced RCC**

Merck KGaA and Pfizer Inc. reported positive top-line results from the pivotal phase III JAVELIN Renal 101 study evaluating avelumab (BAVENCIO) in combination with axitinib (INLYTA) compared with sunitinib (SUTENT) as initial therapy for patients with advanced renal cell carcinoma. As part of a planned interim analysis, an independent Data Monitoring Committee confirmed that the trial showed a statistically significant improvement in progression-free survival (PFS) by central review for patients treated with the combination whose tumors had PD-L1+ expression greater than 1% (primary objective), as well as in the entire study population regardless of PD-L1 tumor expression (secondary objective). According to the statistical analysis plan, if PFS was statistically significant in the PD-L1+ subgroup, then PFS in the entire study population was to be analyzed for statistical significance. JAVELIN Renal 101 will continue as planned to the final analysis for the other primary endpoint of overall survival. Merck and Pfizer intend to pursue a regulatory submission in the U.S. based on these interim results, and these results will be discussed with global health authorities. A detailed analysis will also be submitted for presentation at an upcoming medical congress.

**New Drug Application submitted for urothelial cancer agent**

The Janssen Pharmaceutical Cos. of Johnson & Johnson announced that a New Drug Application has been submitted to the FDA seeking approval of erdafitinib for the treatment of patients with locally advanced or metastatic urothelial cancer and certain fibroblast growth factor receptor (FGFR) genetic alterations whose tumors have progressed after prior chemotherapy. Erdafitinib is an investigational, once-daily, oral pan-FGFR inhibitor that received Breakthrough Therapy Designation from the FDA in March 2018. The NDA submission is based on data from the BLC2001 (NCT02365597) phase II clinical trial, which evaluated the efficacy and safety of erdafitinib in the treatment of adult patients with locally advanced or metastatic urothelial cancer, whose tumors have certain FGFR alterations. The primary endpoint was the percentage of participants with objective response, defined as complete response or partial response based on Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 criteria.

**Stricture device receives financing, FDA approval of U.S. study**

Urotronic has raised $20 million in a strategic round led by HM (Hillhouse & Mayo Clinic) Ventures to support the growth of the Optilume drug-coated balloon, a two-pronged approach to treatment of urethral stricture. In clinical trials performed both in Latin America and the United States, Optilume has performed as intended in both opening blockages and inhibiting the formation of scar tissue that can develop quickly after any medical intervention. The procedure can be performed in an outpatient setting. Urotronic also announced that it has received FDA approval to begin its second U.S. study of Optilume. The latest U.S. Investigational Device Exemption Pivotal clinical study, titled ROBUST III, will enroll up to 200 men from 20 clinical sites across the U.S. and will start immediately. The first FDA-approved U.S. trial of the Optilume for an Early Feasibility Study began in November 2017 and is currently underway in five medical centers around the country.

**Drug developer licenses novel gene therapy for overactive bladder**

Urovant Sciences has licensed a novel investigational gene therapy for patients with overactive bladder symptoms who have failed oral pharmacologic therapy. Urovant has licensed global rights for the development and commercialization of hMaxi-K from Ion Channel Innovations. There are no currently available FDA-approved gene therapy treatments for overactive bladder, according to Urovant. hMaxi-K has been evaluated in two phase I studies in OAB patients, including a small, double-blind, placebo-controlled phase Ib clinical trial as an intravesical injection in women with overactive bladder symptoms. Ion Channel Innovations completed the phase Ib study in 2017 and found hMaxi-K to be generally well tolerated. Clinical results of the trial, which included a limited number of patients (n=13), indicated dose-dependent improvements in urinary urgency and frequency, achieving statistical significance (p<.05) in the high-dose cohort.

**Government funding awarded for investigational IC/BPS agent**

Alivio Therapeutics, an affiliate of PureTech Health plc, announced a $3.3 million U.S. Department of Defense Technology/Therapeutic Development Award to advance Alivio’s product candidate, ALV-107, for the treatment of interstitial cystitis/bladder pain syndrome (IC/BPS) with Hunner's lesions. The funds will support Alivio’s preclinical research and development activities, including GMP manufacturing, to enable the filing of an investigational New Drug Application for ALV-107. Alivio’s platform technology has demonstrated proof-of-concept in 10 different preclinical models of inflammation, including a validated preclinical model for the treatment of IC/BPS. ALV-107 showed durable pain control throughout a 24-hour study period in this model of IC/BPS, lasting at least 12 times longer than lidocaine at a comparable dose (ALV-107, 16 mg/kg; conventional lidocaine, 16 mg/kg).

**Cancer cell phenotypic test predicts PCa adverse pathology**

Cellanyx and clinical collaborators have published the first studies demonstrating the potential of a novel, live cancer cell phenotypic test to predict adverse pathology and allow risk stratification of patients with solid tumors such as prostate and breast cancer. This first-in-class, live tumor cell phenotypic test is designed to provide actionable information on cancer aggressiveness to support shared clinical decision-making. The study, which was published in *Nature Biomedical Engineering*, reports initial results from the analytical validation of the test from a multicenter, blinded clinical study of prostate tissue samples from patients who had undergone radical prostatectomy. The authors additionally describe preliminary results from a separate proof-of-principle study in breast cancer patients undergoing surgery. Predictive metrics from the live tumor cell phenotypic analysis were compared with the conventional post-surgical adverse pathology findings to establish the test’s sensitivity and specificity. Results showed that the Cellanyx generated superior results in predicting adverse pathologies with sensitivity and specificity of more than 80% (ROC ≥80%) and separated patients into distinct, quantifiable groups based on predicted adverse pathology features.
New Products & Services

Stone device enables simultaneous ureterscope, basket use

Boston Scientific has announced the global launch of the LithoVue Empower Retrieval Deployment Device, designed to be used with the LithoVue Single-Use Digital Flexible Ureteroscope and compatible nitinol retrieval basket to enable urologists to operate a ureterscope and basket simultaneously when retrieving kidney stones via flexible ureteroscopy. Data presented by Kevin Koo, MD, showed the LithoVue Empower Device permitted a single surgeon to perform flexible ureteroscopy with stone manipulation and retrieval, using less muscular workload than a single-surgeon ureteroscopy (ie, where a single surgeon has to operate both the ureterscope and retrieval tool) and similar workload to two-surgeon ureteroscopy. Task completion time was also improved with LithoVue Empower over the single-surgeon model and similar to the two-surgeon model, according to Boston Scientific.

For more information, visit www.bostonscientific.com.

At-home testosterone enanthate injection earns FDA approval

The FDA has approved subcutaneous testosterone enanthate (Xyosted) injection, according to manufacturer Antares Pharmaceuticals, Inc., the agent is the first FDA-approved subcutaneous testosterone enanthate product for once-weekly, at-home self-administration with an easy-to-use, single-dose, disposable Quick-Shot auto injector. Testosterone enanthate has been approved in three dosage strengths—50 mg, 75 mg, and 100 mg—and is indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

For more information, visit www.antarespharma.com.

FDA approves radiotherapeutic treatment for adrenal tumors

The FDA has approved the New Drug Application for iobenguane I 131 (AZEDRA), 555 MBq/mL injection for intravenous use. Iobenguane I 131, a radiotherapeutic, is indicated for the treatment of adult and pediatric patients 12 years and older with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy. Iobenguane I 131 A is the first and only approved therapy for this indication, says manufacturer Progenics Pharmaceuticals, Inc.

For more information, visit www.progenics.com.

Patient-focused book outlines male urologic conditions, treatments

In “How’s It Hanging? Expert Answers to the Questions Men Don’t Always Ask,” urologists Neil Baum, MD, and Scott Miller, MD, use humor, analogies, illustrations, and case examples to share their knowledge of the penis, prostate, and testicles. The book discusses the male anatomy, as well as conditions such as erectile dysfunction, premature ejaculation, cancer, testosterone deficiency, and sexually transmitted diseases, and how they can be treated. The book’s aim is to help men make informed decisions about their medical care, according to Skyhorse Publishing.

For more information, visit www.skyhorsepublishing.com.

Cuff stops urinary leakages in prostate cancer patients

The Pacey Cuff is a urethral control device that stops urinary leakages and reduces the dependency on absorption pads by up to 100% in men who have undergone prostate cancer treatment. According to manufacturer Pacey MedTech Ltd., the cuff is more comfortable than traditional penile clamps as it maintains consistent and effective blood flow to the penis. The Pacey Cuff is designed for compression of the urethra to minimize leakage and also to protect the blood circulation in the topside of the penis, eliminating possible bleed supply restriction pain. The cuff was created to be light, soft, and comfortable to ensure patients can discretely wear it all day, continue to live a normal life, and engage in regular activities, the company says.

For more information, visit www.paceycuff.com.

Web platform facilitates provider engagement in advocacy

Revenue cycle management services provider Zotec Partners has launched an advocacy platform that allows users to take action on state and federal legislation that directly impacts their health care business. The website gives users intuitive and easy ways to engage in public policy, in the simple click of a button, with options to send pre-written updates and grassroots alerts directly to state and federal legislators, post social media messages directly to their appointed representatives, or reach out to them via phone or email with a call to action.

For more information, visit www.zotecpac.com.

Artificial intelligence-enabled features improve patient flow

Compulink Healthcare Solutions has introduced new artificial intelligence (AI)-enabled features to its EHR and practice management systems. Called Advantage SMART Practice, it uses AI technology and real-time data from the clinic to completely automate tasks such as billing, along with eliminating steps to improve patient flow. AI-driven enhancements include Advantage SMART Workflow, which lets providers and staff know who is waiting, where they need to go next, and keeps them constantly informed; and Advantage SMART Patient Engagement, which automatically communicates personalized content directly to the patient’s mobile device.

For more information, visit www.compulinkadvantage.com.
What factors reduce the time you spend with patients?

Our time with patients is very truncated. EMRs actually get in the way of good care. They consume huge amounts of time. They take away, directly, from being able to sit with the patient, listen to them, and provide all the needed care. We are not able to give quality time to patients.

During clinic, we actually took a close look at this and found that for every 15-minute clinic visit, we spend 9 minutes on the computer doing what’s required by regulation, billing, or administration to finish notes for that patient. So a 15-minute visit is consumed with 8 or 9 minutes on the computer, and patients end up getting the short end. To keep it from being even worse, we spend a couple of extra hours every night afterwards completing the charts.

To try to keep patients from feeling shortened, I’ll sit and listen to them, and won’t start doing EMR for at least 4-5 minutes—just to hear them out. I’m consciously aware of the time crunch, because if I spend much more than that I won’t have time to do what’s required on the EMR. If I had more time, I’d actually be able to listen to them—just be in the moment with them.”

Huad Frazier, II, MD / Washington

Mostly two things interfere with our patient time: the volume of patients and EMRs. We’re dealing with baby boomers and there are fewer urologists—more retiring with fewer coming out.

We’ve probably done two things to help us provide good patient care. We’ve embraced physician extenders to take some of the burden off, mainly to help patients who need to be seen on a more urgent basis. This allows more patients to get in. We’re still learning that process, but we’ve tried to embrace that.

The other adjustment we’ve made—mostly when we start getting behind—is to put EMR documentation to the side and finish our notes once we’ve finished with clinic—a lot of after-hours work.

It’s harder to do the EMR after hours. You definitely have to take good notes while you’re talking to patients because if you put it off more than a few hours, your notes won’t be as thorough or as accurate. Depending on the volume of patients you see, it’s hard to remember what you said to which patient. You really need to do them that night so you can keep them straight. They have to be done at some point, but you don’t want to sacrifice taking care of the patient.”

Brian Wade, MD / Birmingham, AL
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AUA, AACU back Good Samaritan legislation

Bill protects providers who volunteer during emergencies

Organizations representing urologists are urging Congress to enact protections from medical liability lawsuits for medical professionals who volunteer during emergencies, such as natural disasters or other large-scale crises.

“The AUA and the AACU are backing the Good Samaritan Health Professionals Act, which has been introduced by Rep. Marsha Blackburn (R-TN) and Sen. Bill Cassidy, MD (R-LA). “When a national crisis or catastrophe such as a hurricane, wildfire, flood, or even a terrorist attack occurs, a prompt and adequate medical response can be the difference between life and death, especially for those victims in critical condition,” a statement by the AACU said. “But while physicians and other health care professionals are often willing and eager to assist disaster victims, many have been turned away or otherwise deterred from volunteering due to inconsistent and ambiguous state and federal laws.”

What the bill would do

The proposed legislation seeks to address this situation by eliminating liability for health care professionals who serve as volunteers in response to a federally declared disaster. It would prevent a health care professional from being held liable under federal or state law for harm caused by any act or omission if:

- the professional is serving as a volunteer in response to a disaster
- the act or omission occurs during the period of the disaster, in the professional’s capacity as a volunteer, and in a good faith belief that the individual being treated is in need of health care services.

The bill limits its protections to individuals treating victims in an event that has officially been declared a federal disaster and will not apply in cases of willful, criminal, or reckless misconduct, gross negligence, conscious flagrant indifference, or intoxication by the professional while volunteering.

“With bipartisan support, this bill will help ensure that victims of national disasters... will have access to the quality onsite care they need by enhancing clarity regarding the patchwork of state laws encouraging medical volunteerism and reducing risk and uncertainty for health care professionals.”

AUC STATEMENT

“With bipartisan support, this bill will help ensure that victims of national disasters, such as the recent hurricanes in Puerto Rico, Texas, and Florida, will have access to the quality onsite care they need by enhancing clarity regarding the patchwork of state laws encouraging medical volunteerism and reducing risk and uncertainty for health care professionals,” the AUC said, urging members of Congress to cosponsor the legislation—HR. 1876 in the House and S. 781 in the Senate.

Meanwhile, the AUA said it is running a grassroots campaign asking its members to urge members of the House and Senate to support the legislation and to include it in the Pandemic and All-Hazards Preparedness Reauthorization Act (PAHPA), which will reauthorize a program first enacted in 2006.

“We are asking that you please contact your Senators and ask them to cosponsor S. 781... and to support including this bill language in the PAHPA. We are also asking that you share this information with your colleagues and have them reach out to their Senators as well,” the AUA said in a Policy and Advocacy Brief.

The AUA’s campaign follows up on 11 urologists’ visits to Capitol Hill on this bill and other issues during the Alliance of Specialty Medicine Fly-In in late July. Meeting with lawmakers in both the House and Senate were AUA Legislative Affairs Committee Chairman Tom Rechtschaffen, MD, and committee members Robert Bass, MD, Ron Davis, III, MD, Matt Gettman, MD, Jason Jameson, MD, Jeremy Shelton, MD, and C.J. Stimson, MD, JD; Holgrew Fellow Kev-in Koo, MD; AUA Quality Improvement & Patient Safety (QIPS) Committee Chairman Tim Averch, MD, QIPS committee member John Lam, MD, and Ruchika Talwar, MD.

In introducing the Good Samaritan Health Professionals Act, Dr. Cassidy stressed the importance of medical volunteers in times of disaster. “Volunteers were crucial in helping families begin recovering after last year’s flood,” Dr. Cassidy said. “Following Hurricane Katrina, medical professionals from across the U.S. came to Louisiana to help. The Good Samaritan Health Professionals Act provides medical professionals with legal protections that protect volunteers aiding disaster victims.”

He pointed out that the Volunteer Protection Act of 1997 protects volunteers from nonprofit agencies and government entities from litigation and economic losses resulting from volunteerism, but does not apply to independent volunteers or those who cross state lines to volunteer.

PAHPA reauthorization

Reauthorization of the PAHPA, to which the AUA hopes to add the Good Samaritan bill’s language, was the subject of a House Energy and Commerce Committee hearing in June. Authored by Rep. Susan Brooks (R-IN) and Rep. Anna Eshoo (D-CA), it will reauthorize preparedness and response programs such as the Hospital Preparedness Program, Temporary Reassignment of Federally Funded Personnel, the National Advisory Committee on Children and Disasters, and the Emergency System for Advanced Registration of Volunteer Health Professionals.

Among its provisions, the bill prioritizes preparing for and responding to cyber threats and provides resources for the development of medical countermeasures for pandemic influenza and emergency infectious diseases within Biomedical Advanced Research and Development Authority.

In its appeal to members to contact lawmakers on behalf of the Good Samaritan legislation, the AUA positioned it as part of the medical liability reform initiative, which has been ongoing in Congress for many years.
Delayed abscess Dx results in paralysis
ER doctor suspected stone was causing back pain

Ms. Perko is an attorney in the Columbus, OH office of Reminger Co., LPA, where she specializes in medical malpractice defense litigation and transactional matters. She welcomes your feedback on this column at APerko@reminger.com.

ACACIA BRUSH PERKO, ESQ.

On May 21, a 28-year-old male presented to the hospital with significant upper back pain, with no history of injury. He reportedly informed the medical staff that he recently had an abdominal methicillin-resistant *Staphylococcus aureus* (MRSA) infection and that he was taking an antibiotic. He was discharged with a diagnosis of muscle strain.

On the evening of May 22, he returned to the emergency room with worsening thoracic pain, which was wrapping around to his left flank. He claimed he told the triage nurse of his recent MRSA infection and oral antibiotic. An ER doctor suspected a kidney stone, which was then ruled out by a pelvic computed tomography scan. The patient was administered intravenous morphine and an anti-inflamatory. He was discharged with a diagnosis of back pain.

The following night, he returned to the hospital with continued back pain. While in the ER, he developed leg numbness and weakness that progressed to paralysis. He was diagnosed with a spinal epidural abscess and transferred to another hospital, where he underwent surgery to remove the abscess.

After the patient’s abscess was surgically removed, he remained hospitalized for 2 weeks. He was treated with inpatient rehabilitation for 6 weeks. He suffered incomplete paraplegia with muscle spasms and bowel and bladder dysfunction. Upon discharge, he was treated with physical therapy, which he will do indefinitely, and consulted with a physiatrist, neurologist, urologist, and hematologist.

He was treated with a neurotoxin for muscle spasms and underwent intrathecal baclofen therapy to control them. He further treats with self-catheterization and is on a bowel program. He can only walk a few steps with braces, and is primarily wheelchair-bound.

Medical record noted infection

The patient sued the hospital and physicians who treated him, alleging they were negligent in failing to properly diagnose the spinal abscess. The ER doctor who suspected a kidney stone testified that a spinal abscess would have been high on his differential diagnosis if he had known of the recent MRSA infection. The plaintiff’s counsel introduced medical records in which the nurses and other physicians noted the recent MRSA infection, and the ER doctor conceded that he would have had access to those records at the time he treated the patient.

The plaintiff’s expert opined that the ER doctor should have ordered a magnetic resonance imaging scan on May 22, which would have revealed the abscess, allowing for timely and proper treatment, and would have likely avoided subsequent neurologic injury. The plaintiff’s expert criticized the ER doctor for failing to take an adequate history and physical examination of the patient, who had been diagnosed with a MRSA skin infection on his abdomen that had been recently drained. Had the physician known about the patient’s MRSA, the expert opined, it would have raised a red flag to suggest that the patient’s back pain was a potential infection, which would have necessitated an MRI.

The plaintiff’s expert further opined that when the ER doctor did not find any urinary/gallbladder stones on the CT scan, he assumed that the patient’s back pain was soft tissue/muscular in nature, without considering another source. “Abdominal stranding” was found on the scan, which can indicate inflammation moving toward the spine. However, according to the plaintiff’s expert, the ER doctor failed to look at the abdomen and should have ordered additional testing in order to rule out the kidney stone as a potential source of pain. The ER doctor himself testified that had he known about the MRSA infection, he should have had ordered additional testing.

The evidence that the MRSA infection was contained in the notes likely undercut the ER doctor’s defense, even though he testified that the patient did not exhibit other signs of an abscess, including a fever. The plaintiff presented testimony from a life care expert and economist who presented a life care plan with an approximate present value of $5 million. This testimony ultimately weighed in the patient’s favor.
Most common adverse events reported include hematuria, dysuria, micturition urgency, pelvic pain, and urge incontinence. Most symptoms were mild to moderate in severity and resolved within two to four weeks after the procedure.
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