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INSIDE THIS ISSUE

Is it Still Safe to Treat Overactive Bladder Syndrome with Antimuscarinics?

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Issues related to chronic medication ingestion and subsequent central nervous system disorders ranging from mild cognitive decline to fully developed dementia have now been reported with multiple drug classes. The most common groups managed by functional urology also manifest complicating factors upon which medication effect and side effect can be superimposed, including advanced age, diabetes, tobacco ingestion and other central nervous system and psychiatric disorders. These comorbidities occur in up to a third of cases of defined dementia.

It has now been well reported that anticholinergic drugs as unique agents or when administered in combination with other drugs with anticholinergic activity ("anticholinergic load") can contribute to and potentially exacerbate the progression of cognitive decline and dementia. The mechanism of action for the cognitive side effects of anticholinergic drugs relates to the blockade of neurotransmitter release (specifically acetylcholine) in the central and peripheral nerve systems, and this effect can be mimicked by a variety of compounds.

Co-administered drugs contributing to the drug load include antidepressants, agents with antihistaminic activity, and medications used for the lower urinary tract and gastrointestinal system. It has been well established that many of these medications have shorter term adverse events including somnolence, confusion and even memory disturbance in addition to the risk of cognitive decline leading to dementia.

There have been several observational studies of drugs with anticholinergic activity and potential instigated dementia risk. However, these studies have been hampered by methodological issues such as length of followup and sample size. Two recent trials have attempted to reduce these methodological concerns.

Gray et al found that cumulative total anticholinergic drug ingestion was indeed associated with a modified risk of the development of dementia when considering all drugs with anticholinergic properties.[1] The value of this study was that it did not include drugs prescribed for dementia within the 12 months before patient assessment in the study population. Richardson et al attempted to evaluate different types of medications with anticholinergic properties and found the potential for significant difference in effect among these medications in terms of cognitive risk.[2]

Coupland et al recently reported a large-scale assessment of a population representative of the general United Kingdom population.[3] The study goals were to assess risks of dementia associated with different types of medications with anticholinergic properties using prescription analysis for

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Can MRI Replace Repeat Biopsy during Active Surveillance?

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Use of magnetic resonance imaging (MRI) to guide prostate biopsy (MRI-GB) began 10 to 15 years ago, around the time active surveillance (AS) started to gain widespread adoption. The 2 modalities of the imaging and the management strategies evolved in parallel and have intersected in a game-changing manner. They have been used together at UCLA

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Overactive Bladder Syndrome and Antimuscarinics

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up to 20 years before the diagnosis of dementia. The authors used a nested case control method to assess the risk of dementia in 58,000 patients and compared it to 225,000 controls, all of whom were 55 years old or older. Exposure was assessed using the daily standardized dosing of various anticholinergic drugs prescribed from 1 to 11 years before the diagnosis of dementia and then these exposures were matched to the control group to determine odds ratios for the development of dementia.

Based on exposure there was a clear and significant trend toward the development of the risk for dementia for higher exposure groups based on total daily dosing of medications. Significant increases in the diagnosis of dementia for unique drug classes included those associated with antidepressants, anti-Parkinson's drugs, antipsychotics, antiepileptic drugs and bladder antimuscarinic drugs (odds ratio 1.65). Even with the variable of length of exposure a correlation remained between average daily dosing and dementia development.

Earlier occurring dementia (patients diagnosed before age 80 years) had an even higher association with drug ingestion and development of dementia than did dementia in patients older than 80 years. This strong association indicated that efforts should be made to reduce exposure to drugs with anticholinergic properties in middle-aged as well as older populations.

This most recent trial presents a concerning conundrum for the treatment of storage disorder in the lower urinary tract, historically dependent on the antimuscarinic class of drugs as a mainstay. As this class has increasingly entered the generic realm, cost basis pharmaceutical use has led to even higher rates of ingestion of these drugs for various symptomatic functional lower urinary tract disorders such as urgency, frequency and urge incontinence, or overactive bladder (OAB).

The accruing data certainly would suggest that there is concern related not only to cumulative anticholinergic load, which has been well established, but also with unique drug classes and their impacts on the central nervous system. Similar concerns have been raised with other types of urological disease that do not depend on the inhibition of acetylcholine for action in a recent report related to long-term exposure to an alpha blocking agent for symptomatic benign prostatic hyperplasia.

For practicing urologists the message here is clear not only in terms of practitioner awareness but also for appropriate informed consent, especially for patients most at risk and who represent the most commonly prescribed demographics, those being the middle-aged and older populations who most commonly experience the symptoms compatible with the overactive bladder syndrome. The principles of informed consent would imply that there is no definitive ability to predict the risk of these concerns for each unique individual. However, these population studies should now be included in the discussion as to whether a patient should consider long-term antimuscarinic use.

These findings give us pause as we reconsider the established recommendations that form the treatment algorithm for OAB. The American Urological Association guidelines still suggest behavioral and lifestyle therapy associated with some pelvic floor rehabilitation as the initial steps. The guideline algorithm provides drug therapy as a second step and specifically mentions the antimuscarinic class of drugs.

The findings noted here clearly call for a reconsideration of dependence upon the antimuscarinic class from a standpoint of initial exposure and may call for consideration of the available alternative beta-3 class as potentially being the most reasonable prescription for the at risk population. Importantly, the other potential consideration for practicing physicians is whether to consider a change in the algorithmic approach to OAB with the potential for a compression in the time frame for drug exposure to decision related to progression to tertiary therapy (neuromodulation and neurotoxin administration).

Clearly more data are needed to answer these questions, but the concerns are now definitively established and can only be answered with further evidence. Individual clinicians should be aware of these concerns and should include them as part of the informed decision making discussion with patients with functional lower urinary tract disorders such as overactive bladder. ◆

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3. Coupland CAC, Hill T, Dening T et al: Anticholinergic drug exposure and the risk of dementia: a nested case-control study. JAMA Intern Med 2019; **179**: 1084.

Replacing Repeat Biopsy with MRI

▼ Continued from page 1

prospectively since 2009 resulting in a somewhat unique database of nearly 900 men followed in AS with MRI-GB. An important finding is that biopsy may be deferred in some instances when MRI is negative during AS followup.

The experience upon which selective biopsy deferral is based was recently published.[1] When the UCLA prebiopsy MRI program began in 2009 the accuracy of MRI in prostate cancer diagnosis was unknown.[2] Therefore, from the outset biopsy was performed on clinical grounds (eg prostate specific antigen [PSA], nodule) regardless of MRI findings.

When a lesion was seen on MRI, targeted biopsies were included but systematic sampling was always performed even if MRI showed no lesions. Thus, the imaging was used as a dependent variable to determine its accuracy. Through an experience that now totals more than 4,000 targeted biopsy procedures including hundreds with whole mount correlations, an understanding of the MRI false-negative rate (at least 15% to 20%) became apparent[3] and the value of combining targeted and systematic sampling was ascertained.[4]

When this approach was applied to men on AS the value of MRI-GB in that situation was clarified.[1,5] Historically, using ultrasound (US) guided biopsy, approximately a third of men left AS in the intermediate term because of disease progression. However, when MRI-GB is used to confirm entry criteria (ie low risk), disease progression, more properly called disease reclassification, becomes much less common. MRI-GB confirming low risk reduced the chances of a later upgrading to Gleason Grade Group (GG) 3 or more to less than 12% at followup for as long as 7 years.[1]

Furthermore, 2-year followup from the ASIST (Active Surveillance Magnetic Resonance Imaging Study) randomized trial shows MRI-GB results in 50% fewer failures of AS and less progression to higher grade cancer compared to conventional US guided biopsy.[6] These findings strongly suggest that AS should begin with MRI-GB and that when it does the chance of that man requiring active intervention is small, at least in the intermediate term.

With accurate tissue characterization at the start of AS, how then should followup evaluation be obtained? In the original AS studies such as those at Johns Hopkins in the 1990s ultrasound guided biopsy was performed on every patient every year. That intensity of followup is now considered unnecessary since up-front tissue characterization via MRI-GB has improved.

During followup repeat sampling of the cancerous sites within the prostate (ie tracking biopsy) has become the key to detecting pathological progression. Tracking of specific biopsy site locations is possible with modern MRI-US fusion devices and the validity of tracking biopsy has been confirmed.[7] Most instances of advancing pathology are detected by resampling known tumor sites (fig. 1).

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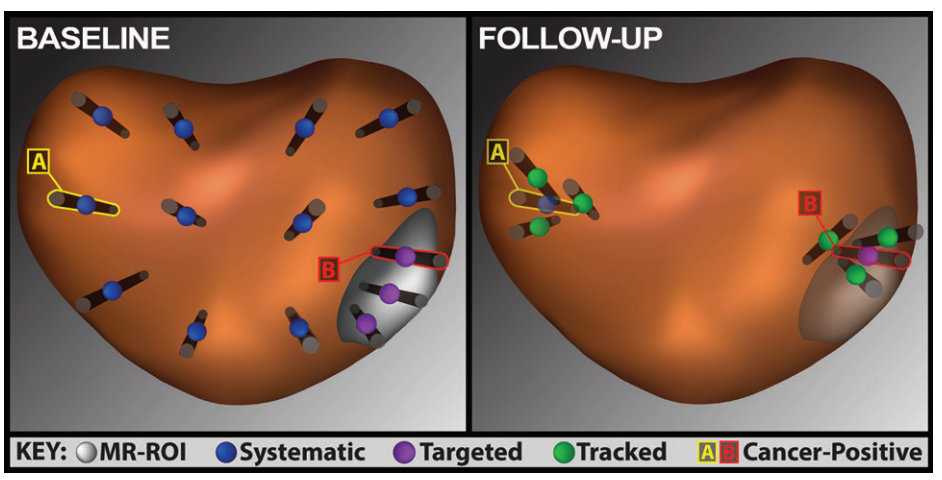

Figure 1. Reconstructed prostate images from fusion device. Gray area is MRI visible region of interest (MR-ROI). Initial biopsy shows systematic (*A*) and targeted (*B*) biopsies with cancer containing cores noted. Followup biopsy shows tracked cores obtained from positive site in systematic *(A)* and targeted (*B*) biopsy.

Replacing Repeat Biopsy with MRI

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Tracking biopsy may be targeted at cancerous sites within the original MRI visible lesion or in a spot that MRI fails to detect. In some 20% of patients subsequent MRI may suggest pathological progression of a preexisting lesion (fig. 2). In such instances targeted biopsies of the lesion can be confirmatory. Only rarely after MRI-GB has confirmed a low risk lesion and AS commences does a followup MRI disclose a different lesion, which proves to be GG3 or more on targeted biopsy (fig. 3).

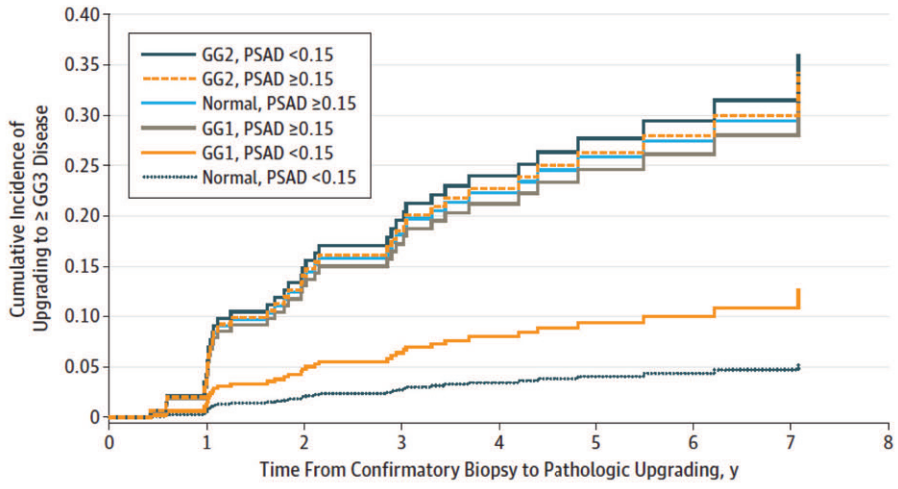

Figure 3. Cumulative incidence of upgrading to GG3 (or more) during years of AS for low risk prostate cancer. When confirmatory biopsy by MRI-US fusion reveals no cancer or only GG1 lesion and PSAD is low (less than 0.15) (bottom 2 lines), chance of upgrading out to 7 years of followup is 10% or less.

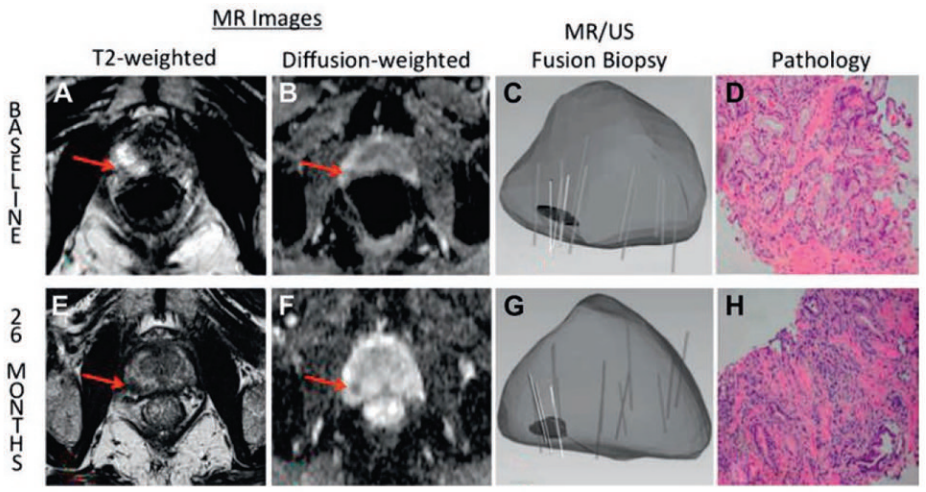

Figure 2. Example of serial MRI used to indicate progression of low risk lesion. Axial T2-weighted image (*A*) demonstrates hypointense lesion in right apical peripheral zone. Diffusion weighted image (*B*) indicates apparent diffusion coefficient of 1,128. Overall PI-RADS score is 3. MRI-US fusion biopsy (*C*) revealed Gleason 3+3 cancer in target (*D*). After 26 months index lesion appears larger (*E*) and apparent diffusion coefficient decreased to 916 (*F*). PI-RADS score is now 4. Repeat targeted biopsy (*G*) reveals Gleason 3+4 *(H)*. Thus, serial MRI indicated more suspicious lesion than noted at baseline and repeat biopsy confirmed disease progression. Tracking biopsy of original cancerous site could have been performed without repeat MRI (fig. 1).

Thus, repeat MRI in the next few years after MRI-GB confirmation of low risk disease may have incremental value[5] but does not compare in value to tracking biopsy.[1] However, when AS is being used for a GG2 lesion or if other risk factors are present the value of sequential MRI may be increased. An important further determinant nearly as important as PI-RADS (Prostate Imaging Reporting and Data System) grade is PSAD (PSA density). The combination of a negative MRI and a low PSAD (less than 0.15) appears to provide additional evidence against the presence of clinically significant prostate cancer.[1] ◆

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Incontinence after Prostate Treatment Guideline Highlights

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Urinary incontinence after prostate treatment (IPT) is an iatrogenic problem caused by an intervention for prostate disease (usually cancer). Risk factors for incontinence in patients undergoing treatment for prostate conditions are well-known. There are also multiple treatments available for this malady.

This guideline summarizes current evidence regarding IPT and provides specific guidance for patients as well as surgeons who treat prostate conditions that can lead to urinary incontinence and those who treat IPT.[1] Furthermore, it provides guidance regarding evaluation and includes a stepwise algorithmic approach to management.

The patient population referred to in this guideline is patients undergoing radical prostatectomy (RP), radiation therapy (RT) for prostate cancer, surgery for benign prostatic hyperplasia and multimodal therapy for prostate cancer. The guideline is divided into 6 sections.

Before Prostate Treatment

Clinicians should counsel patients undergoing prostate treatment, particularly radical prostatectomy, that urinary incontinence is common but generally resolves by 12 months, and that sexual arousal incontinence and climacturia are possibilities. In addition, clinicians should discuss all known risk factors (current age, prostate size, membranous urethral length and possibly body mass index) for postoperative urinary incontinence. Surgical approach, specifically robotic/laparoscopic vs open, is not a risk factor.

Pelvic floor muscle exercises (PFME) or pelvic floor muscle training (PFMT) may be offered to patients preoperatively. Patients undergoing transurethral resection of the prostate (TURP) or RP after primary RT have a higher rate of urinary incontinence than those who have not had RT. It is important to note that timing of radiation and surgery is important. Patients undergoing salvage or adjuvant RT have better urinary function recovery than those undergoing RP after primary radiation therapy. Similarly, RT for patients who have undergone TURP does not seem to have appreciably higher incontinence rates, but those who undergo TURP after RT have incontinence rates approaching 30%.

After Prostate Treatment

PFME/PFMT should be offered to all patients after RP. This intervention is the most likely to hasten urinary continence recovery for these patients. Patients who have bothersome stress urinary incontinence (SUI) 12 months after RP despite PFME/PFMT should be evaluated for and offered surgical management. Furthermore, clinicians should offer surgical management to patients with stable but bothersome stress urinary incontinence 6 months after RP. This is particularly true for patients with severe incontinence at 6 months and those who have undergone salvage RP.

Evaluation of Incontinence after Prostate Treatment

The category type and severity of incontinence along with degree of bother should be assessed in patients with IPT using a history, physical examination and appropriate diagnostic modalities. Patients with urgency urinary incontinence or urge predominant urinary incontinence should be treated initially as having overactive bladder and offered treatment options as presented in the AUA/SUFU overactive bladder guideline.[2] While stress urinary incontinence should be confirmed by history, physical examination or ancillary testing before offering surgical intervention, a demonstration of provoked incontinence on physical examination is not necessary.

Surgical and nonsurgical management options including pads,

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Advances in Urodynamics: New Research on Methods of Lower Urinary Tract Evaluation

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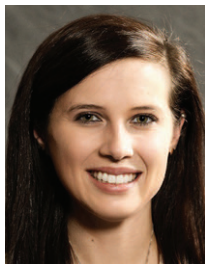

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Urodynamic studies (UDS) have remained the gold standard for objectively evaluating disorders of lower urinary tract dysfunction for more than 50 years. However, UDS technology has not evolved substantially since its introduction into urological practice. Furthermore, the diagnostic capabilities of UDS have been largely limited by the nonphysiological nature of testing, patient discomfort and the overall poor reproducibility of results.

More recently there have been significant strides to modernize UDS as well as decrease its invasiveness. These advances include the ability to collect data outside of the urology clinic as well as the incorporation of novel technologies to evaluate the filling and voiding phases of micturition. We present a brief overview of the most recent advances in UDS technology and the diagnostic utility of these emerging technologies (see Appendix).

Ambulatory Urodynamic Monitoring

A key problem with current UDS technology is that it provides only a snapshot, which may not reflect the patient's typical bladder function. Ambulatory urodynamic monitoring (AUM) offers catheter based measurement of bladder pressure outside of the UDS laboratory. AUM records data continuously to improve capture of transient symptoms and resulting bladder events. In addition, AUM evaluates the lower urinary tract as it fills naturally and may provide a more accurate reflection of the patient's bladder function. AUM has increased sensitivity but lower specificity than standard UDS but further trials are needed before confirming its clinical utility.[1] Moreover, questions surrounding cost and patient safety require further study.

Novel telemetric ambulatory urodynamic monitoring systems are currently under development and aim to improve patient comfort via wireless, catheter-free, battery powered devices to monitor bladder pressure and volume in the privacy of the patient's home. These systems may also allow providers to remotely monitor patient symptoms.[1]

However, current devices are only in the development stage and may require implantation within the bladder lumen. Ambulatory urodynamic monitoring and telemetric ambulatory urodynamic monitoring may improve identification of transient symptoms but are limited by an inability to record volumes (voided and residual) as well as the necessity of an invasive implant.

Emerging Technologies for the Filling Phase

During the filling phase of micturition information provided by current UDS technology is limited to the identification of involuntary detrusor contractions, measurement of compliance, and determination of bladder sensation using episodic and poorly defined verbal sensory thresholds including the "first sensation of filling," "the first desire to void" and a "strong desire to void." However, innovative filling phase technologies are under development.

For example, it has long been observed that the bladder wall experiences varying degrees of low amplitude spontaneous activity or "micromotion." Although current UDS cannot identify and quantitate bladder micromotion, investigators have developed automated algorithms for this purpose.[2] In addition, the use of ultrasound UDS to monitor bladder

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Emerging Lower Urinary Tract Evaluation

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shape change may represent a noninvasive test for the detection of involuntary detrusor contractions.[3]

Ultrasound UDS has also been evaluated as a method to quantitate bladder biomechanical properties of wall tension, stress, strain and elastic modulus that may ultimately be used to identify new subphenotypes of overactive bladder.[4] Moreover, Doppler flow ultrasound studies have determined that patients with lower urinary tract symptoms have significantly decreased pelvic blood flow.

During UDS functional brain imaging using magnetic resonance imaging (MRI) and near infrared spectroscopy (NIRS) can also be used to monitor the micturition cycle by identifying regions of activation/deactivation. Functional MRI provides a 3-dimensional assessment of brain activity during filling but requires specially adapted UDS equipment, performance in a MRI suite and filling/voiding in the supine position.

Functional NIRS is less expensive and can be performed during natural filling but only evaluates cortical neuroexcitation (see figure).[4,5] Finally, the use of a sensation meter has offered more accurate and detailed descriptions of sensation during UDS. This new tablet based device generates sensation capacity curves throughout filling which enables phenotyping of voiding dysfunction.[4]

Emerging Technologies for the Voiding Phase

As part of standard UDS the voiding phase is assessed with a pressure flow study that helps differentiate bladder outlet obstruction (BOO) from underactive bladder. Noninvasive measures of voiding or voiding efficiency are performed using uroflowmetry and measurement of post-void residual volume. While helpful adjuncts to UDS, these tools do not have the predictive power of UDS. In this regard, newer advancements include measuring transmitted pressures after compression and relaxation of the urethra by an external device (eg the penile cuff test and pressure sensing external condom catheter).[6]

Furthermore, there has been significant innovation using ultrasound to aid in the diagnosis of bladder outlet obstruction through the evaluation of detrusor wall thickness, intravesical prostatic protrusion and measurement of resistive indices.[6] In addition, noninvasive Doppler ultrasound can be used to calculate resistive indices with rises demonstrating a high predictive value for bladder outlet obstruction potentially secondary to reduced vascular supply in hypertrophied and obstructed detrusor.

Lastly, bladder NIRS has also shown promise as a novel voiding phase metric. NIRS uses near infrared light to quantify changes in tissue oxygenation, which is coupled to a classification and regression tree algorithm to assess patterns throughout UDS. A nomogram was created using detrusor pressure at maximum flow vs relative concentration of total hemoglobin at maximum flow to classify cases as obstructed or unobstructed.[4]

Conclusion

The field of UDS is evolving with the development of novel technologies to overcome the inherent limitations of UDS and allow for improved phenotyping of voiding dysfunction. Innovations are occurring in the development of ambulatory and wireless devices. In addition, the use of ultrasound and neuroimaging technologies during the filling phase may greatly expand the diagnostic capabilities of current UDS. Finally, novel imaging and compressive technologies may allow for completely noninvasive diagnosis of bladder outlet obstruction in the voiding phase. All of these emerging technologies have common goals of improving UDS diagnostics while limiting invasiveness. ◆

Appendix. Emerging technologies in lower urinary tract evaluation

Technology	Diagnostic Utility
Urodynamics:	
Ambulatory UDS	Continuous monitoring; non-clinical setting
Telemetric Ambulatory UDS	Wireless/remote monitoring; may not need catheters
Filling Phase Technologies:	
Ultrasound UDS	Bladder shape, biomechanics, micromotion, blood flow
Brain functional MRI	3D identification of neuroactivation during UDS
Brain functional NIRS	Cortical identification of neuroexcitation at lower cost
Sensation Meter	Real-time sensation; sensation-capacity curves
Voiding Phase Technologies:	
Ultrasound	Wall thickness, prostate protraction, blood flow in BOO
Penile Compressive Devices	Penile cuff test with external condom catheter in BOO
Bladder NIRS	Hemoglobin concentration vs flow to diagnose BOO

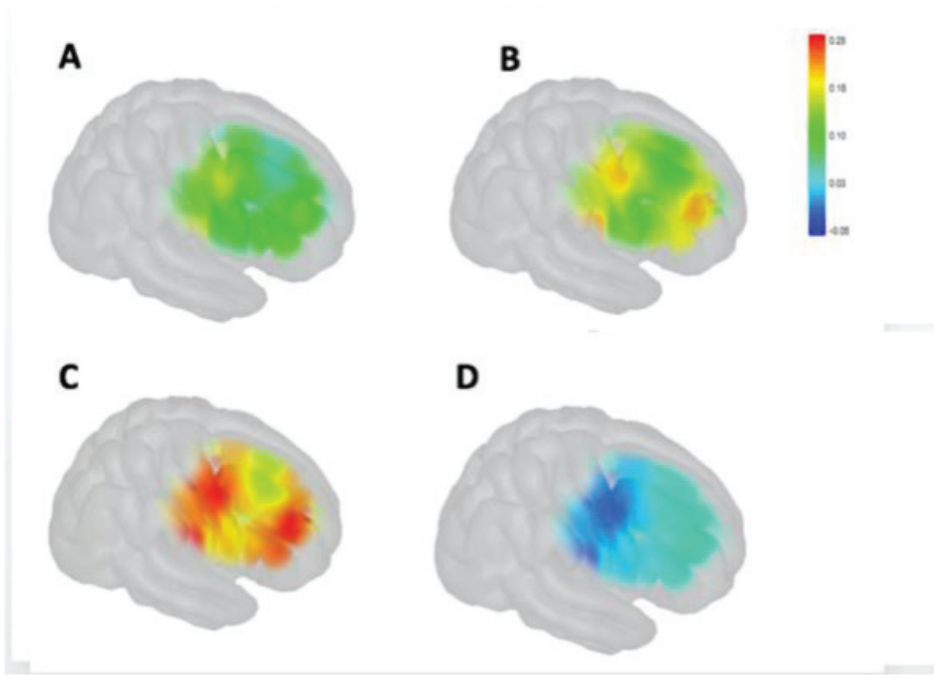

Figure. Example of brain functional NIRS of anterior cortex using simplified 4 x 4 grid shows changes in O_2Hb (neuroexcitation), where color from blue to red indicates increasing intensity, at bladder capacity (*A*), after permission to void (*B*), during void (*C*) and at void completion (*D*).[5]

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Incontinence after Prostate Treatment

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other collection devices and occlusion clamps should be discussed with all patients with SUI. A shared decision making model should be used to discuss risks, benefits and expectations focusing on the degree of bother. For patients who choose surgery for IPT cystoscopy should be performed and urodynamics testing may be used if there is any question regarding management.

Treatment Options

All patients seeking surgical treatment for IPT should be offered PFME/PFMT. If conservative measures fail all patients with bothersome stress urinary incontinence should be considered for an artificial urinary sphincter (AUS). Before implanting an AUS clinicians should confirm that patients have adequate physical and cognitive capabilities to operate the device and are aware of the risks of the device, particularly mechanical failure, infection and erosion. Furthermore, AUS reoperations are common. A single cuff, perineal surgical approach is preferred at the time of initial AUS surgery.

Male slings should be considered for patients with mild to moderate stress urinary incontinence. Expectations of success and risks of failure should be discussed with all patients undergoing a male sling procedure. Note that male slings should not routinely be performed in patients with severe SUI. This guideline does not make a distinction between adjustable and fixed slings.

Adjustable balloon devices can be offered to patients with mild SUI after prostate treatment. These devices are now FDA (U.S. Food and Drug Administration) approved for this indication but experience with them is still quite limited.

Treatment options for SUI after benign prostatic hyperplasia surgery are the same as those for SUI after prostate cancer treatment. However, in patients who have undergone primary, adjuvant or salvage RT an AUS is the preferred treatment.

Finally, urethral bulking agents are not FDA approved for male incontinence and patients should be counseled that efficacy is low and cure is rare after these treatments. All other techniques for IPT should be considered investigational.

Complications after Surgery

Complications such as recurrent or persistent incontinence are common after AUS placement and all patients undergoing these procedures should be told about them. For patients who experience recurrent or persistent incontinence after AUS or sling placement clinicians should again perform a history, physical and any appropriate investigations to determine the cause.

For patients with persistent or recurrent incontinence after male sling placement or an AUS, an AUS should be considered. This guideline provides 2 algorithms for evaluating sling failure and AUS failure. A mechanical failure of an AUS can easily be determined in a patient with recurrent incontinence by measuring volume in the reservoir using cross-sectional imaging. A low reservoir volume means device failure.

Special Situations

An infection or erosion of a male sling or an AUS necessitates removal of the device followed by a 3-month period of healing before reimplantation. Sections on treatment for climacturia, IPT after urethral reconstructive surgery, treatment of IPT with symptomatic vesicourethral stenosis and role of urinary diversion are also included.

The unabridged version of this guideline is available at https://www.auanet.org/guidelines/incontinence-after-prostate-treatment. ◆

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Who Should Undergo Cytoreductive Nephrectomy?

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Cytoreductive nephrectomy (CN) has been considered frontline therapy for patients with metastatic renal cell carcinoma (mRCC) initially based on 2 trials combining interferon alpha with CN. These studies demonstrated superior survival compared to interferon alpha therapy alone, with a combined trial analysis yielding a 6-month benefit in overall survival for the combination arm.

Since these studies were published in 2001 there have been significant advances in systemic therapy including VEGF receptor tyrosine kinase inhibitors (TKIs) and more recently, immune-oncology (IO) agents. Given the advances in systemic therapy the survival advantage attributed to CN has been questioned.

The CARMENA randomized noninferiority clinical trial was published in 2018 and showed that overall survival was noninferior in the sunitinib alone arm compared to CN plus sunitinib.[1] This trial had methodological and recruitment issues making its conclusions less robust. The role and timing of CN remain debated, especially since sunitinib is less relevant as first line therapy in 2020. Certain patients may still benefit from CN, and we outline our selection process for determining which patients are counseled to undergo CN in the setting of modern systemic therapy.

The first step in patient selection is a clear understanding of disease extent and patient goals. All cases must be rigorously staged and there must be an assessment of existing comorbidities and life expectancy. We routinely obtain brain magnetic resonance imaging (MRI) and bone scan (even in the absence of symptoms) in patients with evidence of any metastatic disease, given the risk of under staging.

Additionally, a multiquadrant renal mass biopsy should be considered, particularly for patients with an unusual clinical presentation, potential for a concurrent synchronous primary tumor, or if the biopsy results may guide systemic therapy choice (for example, if sarcomatoid elements are suspected based on imaging). A discussion with the patient regarding treatment goals should be held to address whether CN is being performed for symptomatic/palliative benefit or in an effort to improve survival.

For patients in whom the attempt is to improve survival or delay systemic therapy, stratification occurs according to various risk criteria. Currently the most widely used system is the IMDC (International Metastatic RCC Database Consortium) risk stratification criteria and based on performance status (PS) and serum laboratory test results. It was originally designed to stratify patients with mRCC receiving TKI therapy and is currently used for clinical trial design and treatment selection.

Patients deemed poor risk have the shortest overall survival and may be less likely to derive benefit from CN. However, this system was not specifically designed to select patients who should or should not undergo CN, and caution should be exercised when attempting to use it for CN selection purposes. Several of these risk factors (whether performance status or laboratory studies) could be improved by performing CN if the bulk of the tumor was in the kidney and was resectable.

Culp et al evaluated preoperative prognostic factors (based on clinical, radiographic and laboratory studies) specifically for patients undergoing CN in order to identify those most likely to derive survival benefit following CN.[2] Such risk classification systems may be more relevant in guiding CN patient selection.

In addition to risk classification systems, many prognostic factors have been independently studied to help identify patients who may be more or less likely to benefit from CN. When discussing these factors it is important to recognize that many of these studies were retrospective, have limited or no external validation and are subject to surgeon selection bias favoring healthier patients. In terms of patient characteristics, many studies have evaluated performance status and demonstrated that those with poor performance status are significantly less likely to benefit from CN, unless the performance status is directly related to primary tumor burden.

Additionally, patients with the majority of the tumor burden located within the primary tumor may potentially benefit from CN. In a post hoc analysis of CARMENA at a median followup of 61.5 months the number of metastatic sites was not helpful in defining good surgical candidates, while patients with only 1 IMDC risk factor might benefit from CN.[3] In addition, this post hoc study noted that patients with secondary nephrectomy (those patients who were supposed to be treated with sunitinib only, without CN, but ultimately did undergo CN) had a median overall survival of 48.5 months.

Patients presenting with an inferior vena cava tumor thrombus can be particularly challenging to treat with an up to 4% perioperative mortality rate. Abel et al identified risk factors in addition to the IMDC criteria including level 4 thrombus, sarcomatoid dedifferentiation and systemic symptoms to be independently associated with worse overall survival in a CN population.[4]

Careful selection is critical and those less likely to gain a survival advantage from surgery should be considered for clinical trial or standard systemic therapy. Additional prognostic factors that require further validation include neutrophil-lymphocyte ratio, C-reactive protein, tumor volume and location of metastatic disease (such as brain, bone, liver vs others).

The decision between up-front CN vs initial systemic therapy with delayed CN is controversial. The SURTIME trial attempted to answer this question, demonstrating in the intention to treat population no significant difference in progression-free survival between up-front vs delayed CN in patients treated with sunitinib.[5] However, the trial was limited by incomplete accrual and was not powered to detect overall survival differences.

However, 1 factor consistently shown to aid with patient selection is response to preoperative systemic therapy. Patients who receive preoperative systemic therapy and have worsening performance status or disease progression generally fare poorly, with survival less than 6 months in most phase II clinical trials and retrospective series. These patients do not benefit from surgical intervention and, thus, preoperative systemic therapy can aid in selecting those patients who should not undergo CN.

Alternatively, CN may reasonably be offered to patients with improved performance status or disease stability/partial response after preoperative therapy. However, one could argue that these particular patients may not require CN at all as they are doing well on systemic therapy alone. Unfortunately no clinical trial has addressed this particular question.

Therefore, we presented a trial concept in November 2016 at the 15th International Kidney Cancer Symposium (Cytoreductive Nephrectomy: Yes, No, Clinical Trial?) that combines these 2 questions in 1 clinical trial (fig. 1). All patients with metastatic clear cell renal cell carcinoma would receive the best available systemic therapy at the time instead of specifying a particular drug or drug combination. This would allow flexibility in regimens and accommodate the current fast pace of new therapy approval. The limitation of specifying 1 particular agent in the current era of surgical trial design was demonstrated in the CARMENA and SURTIME trials, given that by the time of their publication, sunitinib was no longer first line therapy in

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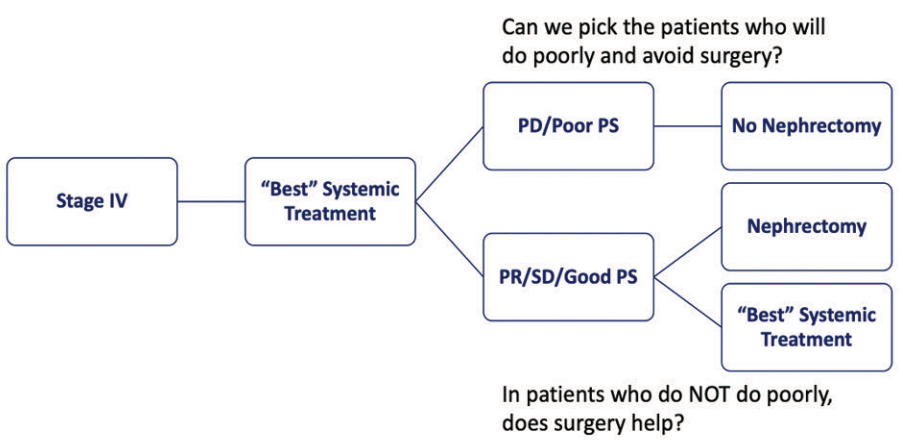

Figure 1. Proposed clinical trial presented at 15th International Kidney Cancer Symposium, November 4, 2016. *PD*, progressive disease. *PR*, partial response. *SD*, stable disease.

Who Should Undergo Cytoreductive Nephrectomy?

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many countries or clinical scenarios.

In summary, patient selection for CN is a highly nuanced process. We present one of many potential approaches for how to treat patients with de novo mRCC with the primary tumor in place (fig. 2). Urologists must approach these decisions in a multidisciplinary setting involving genitourinary medical oncology, while keeping patients' goals in mind through shared decision making.

These decisions have become increasingly complex with the addition of more effective systemic therapy including IO agents. While much progress has been made in treating mRCC, further work is needed to redefine the role of CN, and encourage the design and enrollment into novel clinical trials with a strong translational research component. ◆

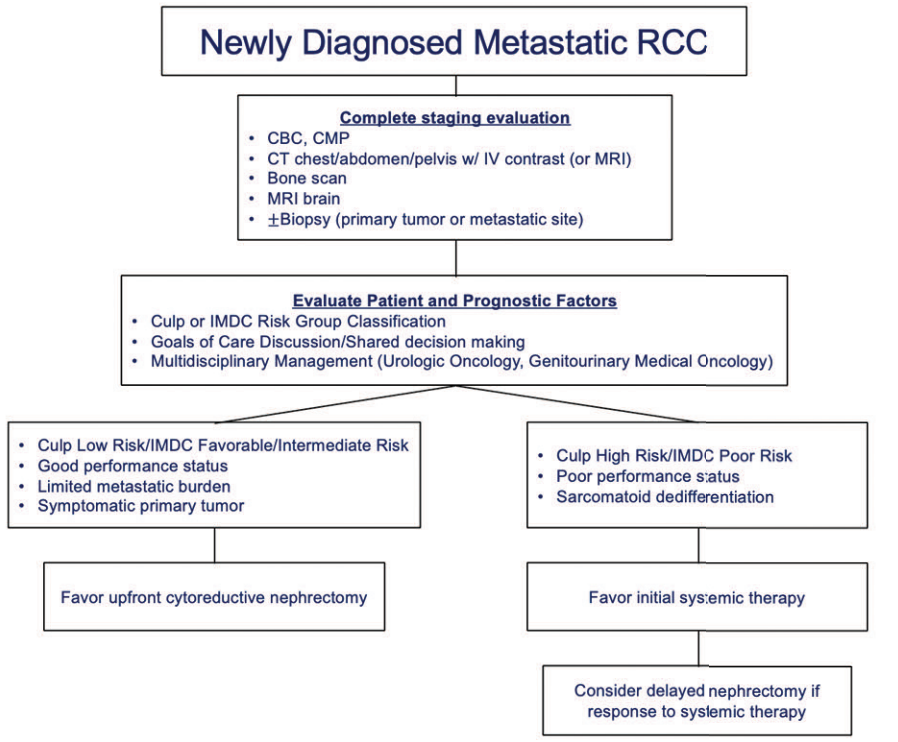

Figure 2. Decision making schema for patients with newly diagnosed mRCC. *CBC*, complete blood count. *CMP*, comprehensive metabolic panel. *CT*, computerized tomography.

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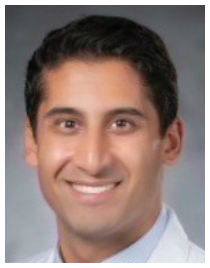
Is Surgery an Outcome of Studies Predicting Surgical Intervention?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Insights from behavioral economists as well as lived experience teach us that humans are irrational.[1] When it comes to medical decision making urologists and patients are no exception. This irrationality is compounded by the fact that our decisions, including the decision to perform surgery, are based on inherently imperfect information including patient values and emotional responses, provider's past experiences, and countless other human factors that are not easily accounted for in decision making tools and clinical care guidelines.[2,3]

It is clear that issues other than disease characteristics and comorbidity impact our decisions to perform surgery. It is equally clear that nonclinical factors such as patient demographics, geography, cost, psychological stress and numerous other intangibles make a difference in the decision to proceed with surgery and/or the timing of surgery.[4-6]

Beyond these intangible factors it is worth noting that it is rare for patients to truly require surgery. An argument can certainly be made for necessary surgery in the case of major trauma or surgically curable, otherwise lethal cancers. However, even these conditions are not absolute criteria. After all, does a 102-year-old great-grandmother truly require surgery to remove her otherwise incurable renal tumor, or is there still room for the human factor of decision making when discussing the merits of operating?

For any individual patient the need for surgery is an imperfect assessment made by irrational human beings based on incomplete information. Perhaps if we were all perfectly rational and omniscient creatures, our understanding of who truly needs surgery would be different. But for better or for worse, urologists and patients are human and therefore hopelessly, helplessly irrational. This fact becomes especially clear when we are faced with tough choices including whether or not to perform or undergo surgery.

Our irrational nature and its impact on surgical decision making can manifest themselves in our clinical research, specifically in the way we design and analyze research studies. Studies that aim to predict surgical intervention too often overlook the fact that surgery is not a natural outcome of any disease process. Rather, surgery is a choice made via a complex combination of rational evidence, biological processes and irrational human decision making.

As sophisticated statistical models and predictive analytics proliferate in urological research, recognizing the distinction between modeling disease outcomes and modeling surgical decision making is paramount. If the goal of a study is to identify factors involved in the decision making process itself, choosing surgical intervention as an outcome is entirely appropriate.

However, all too often statistical models use comorbidities and other biological factors in an attempt to predict whether a patient will ultimately undergo surgery. This type of outcome selection is simply not appropriate in this circumstance. Such predictive models are fatally flawed by their failure to account for the irrational subjectivity that influences the statistical outcome.

To put this more simply, the first step of any research project is to formulate a research question. If that question is, "What factors were associated with a surgeon's (or a patient's) decision to proceed with surgery?" then surgery is an entirely appropriate statistical outcome. If the question instead is, "What factors were associated with a biological need for surgery?" then we strongly believe that surgery is not an appropriate statistical outcome.

The simple reality is that no statistical model can effectively reconcile the idiosyncrasies and irrationality of human decision making with a biological disease process. While this may seem like a matter of semantics, it is crucial to recognize that terminology matters. Specifically, our terminology can have profound effects on how we construct our statistical models and on the validity of their findings.

No amount of statistical wizardry can provide us with correct answers if we ask the wrong questions. A patient requiring surgery and deciding on surgery are not synonymous. Conflating the 2 blinds us to the reality that the decision to perform surgery is complex and is strongly influenced by human factors.

Ultimately, poor quality modeling strategies lend truth to Mark Twain's old adage about "lies, damned lies, and statistics." As we enter a new decade of the 21st century, it is our fervent hope that urologists (and our biostatistical colleagues) are capable of disproving a 19th century

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The Impact of a Penile Prosthesis on Quality of Life

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In the medical arena research has historically centered on objective and concrete data such as treatment efficacy, survival rates and potential adverse effects. Through the years the mind-set has shifted to incorporate aspects of health related to quality of life (QOL) within outcomes research as opposed to solely focusing on the quantity of life.

The introduction of the inflatable penile prosthesis in 1973 provided a safe and effective treatment option for medically refractory erectile dysfunction (ED). Many studies have been published on treatment outcomes, complications and device survival. In line with other research there has been a growing trend toward understanding the impact of the penile prosthesis on a patient's quality of life.

Given the high prevalence of ED and its known relation to psychological distress and virility, it is important that QOL outcomes have come to the forefront. As Caraceni and Utizi eloquently stated, "Because survival is not affected by ED or its treatment, the evaluation of penile prosthesis effectiveness is primarily focused on recipients' QOL, which is the real end point in the evaluation of therapeutic success or failure."[1]

Attempts to quantify QOL pose challenges. The World Health Organization defines QOL as individuals' perceptions of their position in life in the context of culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. These factors are all interrelated with an individual's physical health, psychological state and social well-being.

Needless to say the definition can be subjective and complex. Given the intricacies of the definition, measuring QOL proves difficult in a research setting. Researchers use any number of questionnaires, limiting the ability to compare findings across studies given the differences in assessment. In addition, researchers will group QOL domains simply by "patient satisfaction," although these groups can be further divided into many different and important components.

It is also important to consider a limitation to all of the studies on penile prosthesis and patient satisfaction. All patients have electively undergone the implantation of a penile prosthesis and, therefore, have a selection bias that may affect QOL outcomes.

In a recent study reviewing satisfaction assessments after penile prosthesis 48 articles were identified.[2] The IIEF (International Index of Erectile Function) or EDITS (Erectile Dysfunction Inventory of Treatment Satisfaction) questionnaire was distributed in 44% of the articles, while the majority of articles (56%) used an investigator designed questionnaire.

Beyond the difficulties of comparing outcomes across these studies this statistic underscores yet another challenge in assessing QOL. We are using questionnaires that were not validated or truly applicable for patients who had undergone penile prosthesis placement. For example, portions of the IIEF and EDITS questionnaires inquire into duration of erection and timing of effect, which in theory are patient driven with a penile implant.

A group in Italy sought to address these limitations by designing and validating a questionnaire specifically addressing the 4 main QOL components of functional, relational, social and personal well-being for patients with penile implants.[1] The QoLSPP (Quality of Life and Sexuality with Penile Prosthesis) questionnaire identified that the inflatable penile prosthesis had a positive effect on all domains, including increased confidence with intercourse, improved general well-being, improved relationship with partner and high levels of overall satisfaction. They were also able to show internal validity and stability with their questionnaire.

The urologist is truly in a unique situation to have a large impact on patient physical and mental well-being. The Massachusetts Male Aging Study is often cited for its finding of a combined prevalence of impotence of 52% among noninstitutionalized men 40 to 70 years old. This study not only showed the high prevalence of this disease but also found a statistically significant association of depression and impotence.

The age adjusted probability of moderate or complete impotence was almost 90% in patients at a maximum degree of depression compared with a 25% probability in those who were the least depressed. These staggering statistics show the prevalence of erectile dysfunction and the intimate connection between medical disease and mental well-being. My hope is that the future holds a better understanding of the impact on QOL with standardized research but also that the research leads to improvements in the penile prosthesis that further enhance patient lives. ◆

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Going Narcotic-Free: Minimizing Opioids from Endourology Practice

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As of 2017 there has been an overall reduction in the number of narcotic prescriptions with an almost 19.2% reduction since the prescription of opioids peaked in 2006. However, despite the reduction 56,935,332 people (17.4% of the U.S. population) received 1 or more opioid prescriptions in 2017. What is even more concerning is the 3 million prescriptions filled for children and adolescents less than 18 years old. The third leading cause of death in the United States in 2017 was unintentional injuries, of which almost a third resulted from opioid overdose. In that year it was estimated that 42,249 deaths occurred as a result of prescription and/or illicit opioid overdose.

According to the Centers for Disease Control and Prevention less than 5% of abused opioids were purchased from a dealer.[1] A staggering 88.5% of abused opioids resulted from a prescription (17.3%), or were freely obtained with permission (55%), purchased (11.4%) or stolen (4.8%) from a friend or family. As a result in 2018 Congress passed bipartisan legislation (H.R.6) targeting the opioid epidemic.[2] This legislation mandates that all agencies provide a plan for medical professionals to certify they have obtained training in the prescribing, management and prevention of schedule II medications, namely opioids.

While educating providers on the appropriate use of narcotics to treat pain is vital to successful resolution of the opioid epidemic, there are multiple opportunities to simplify patient care by not using opioids. One area is in the management of acute pain. Although the management of acute pain only represents a subset of the total number of narcotic prescriptions provided annually, there is compelling evidence that reducing the number of opioid prescriptions for acute pain can have immense long-term benefits.

A major source of acute pain is surgery. According to historical data approximately 50 million ambulatory procedures are performed annually in the U.S. Despite misuse and dependence being relatively low after treatment for acute pain (6% to 8% and 0.5%, respectively), the absolute number of lives potentially affected negatively is staggering (1.6 million and 250,000 people, respectively). Perhaps the most important group in this cohort is opioid naïve patients. Among approximately 1.3 million opioid naïve patients undergoing surgery 6% were still consuming narcotics 12 months after exposure and 3% were still using them at 3 years.

In urology there are multiple parallel efforts addressing the topic of opioid stewardship for our patients. The 2018 AUA Quality Improvement Summit was directed at tackling the issue of appropriate narcotics use in our field while generating and disseminating the concept of opioid-free and opioid reduced urological care.[3]

At the forefront of opioid-free surgery are endourologists, seemingly appropriately, given the proclivity toward natural orifice or laparoscopic surgery. Based on research from 2011 showing that 67% of patients reported a surplus of narcotics after a urological procedure, 1 group used text messaging after ureteroscopy (URS) to show that the median opioid consumption was 10 pills, 25% of patients used no narcotics and 63% of all pills went unused.[4] With these publications and in an attempt to simplify care, our group considered the feasibility of performing narcotic-free ureteroscopy (nf-URS).

In October 2018 we published 6-month data showing that nf-URS in 52 patients generated fewer phone calls (17% vs 19%) and fewer secondary narcotic prescriptions (10% vs 17%) compared to 52 control patients who received narcotics.[5] Additionally, there were 20 opioid naïve patients in each group, of whom none in the nf-URS group requested a narcotic prescription compared to 4 (20%) in the standard URS cohort who sought out at least 1 refill after using on average 30 narcotics tablets. Lastly, almost 1,400 narcotic pills were removed from circulation because of the adoption of nf-URS in 6 months by a single surgeon.

Nf-URS is progressively being adopted in the United States. To optimize success many groups are developing and implementing enhanced recovery after surgery protocols that avoid the use of narcotics after URS. The cornerstones of these protocols include extensive patient counseling before surgery, shifting the culture of all providers toward nf-URS as the standard of care, and diligent use of nonsteroidal anti-inflammatory drugs, alpha blockers, anticholinergics, and local anesthetics with occasional use of short-term tapered steroids packs.

As other transurethral procedures (holmium laser enucleation of the prostate, transurethral resection of the prostate, transurethral bladder tumor resection, cystolitholapaxy) are already narcotic-free, the last hurdle in endourology is narcotic-free percutaneous nephrolithotomy. Current efforts to establish enhanced recovery after surgery protocols, optimize regional blocks, use nonnarcotic analgesics and maximize tubeless procedures are underway and will hopefully establish narcotic-free surgery as the new standard of care for endourology.

In conclusion, the efforts of endourologists to stop narcotics use are proving successful and are impacting all of urology. Today there are urologists promoting narcotic-free laparoscopy with evidence to support the concept of nf-robotic assisted laparoscopic prostatectomy. However, for those urologists not quite ready to take on the rewarding challenge of narcotic-free surgery multiple resources are available to offer guidance as to the appropriate type and number of narcotics to use after a variety of urological procedures, for example those available at https://michigan-open.org/.

Despite our inherent desire as physicians to remove any and all suffering for our patients, we all commit to primum non nocere. This concept of first, do no harm has never been more applicable than to the use of narcotics for patients undergoing urological surgery. The long-term potential expense of narcotic exposure far outweighs the benefits of the temporary short-term pain relief achieved by narcotics. ◆

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HAVE YOU *Read?*

Daniel Shoskes, MD
Cleveland, Ohio

Bejan CA, Lee DJ, Xu Y et al: Performance of a natural language processing method to extract stone composition from the electronic health record. Urology 2019; 132: 56-62.

The primary function of the electronic health record (EHR) is documentation to maximize billing. Clinical and research functions are secondary. Although the data vault is big, creative techniques are often necessary to extract useful research information.

The authors sought to demonstrate the utility of a natural language processing (NLP) algorithm for mining kidney stone composition in a large-scale electronic health records repository. Thus, they developed StoneX, a pattern matching method for extracting kidney stone composition information from clinical notes, and trained the algorithm on manually annotated text mentions of calcium oxalate monohydrate, calcium oxalate dihydrate, hydroxyapatite, brushite, uric acid and struvite stones.

StoneX was used to identify patients with kidney stone composition data and to mine more than 125 million notes from the EHR. Analyses performed on the extracted patient data included stone type conversions over time, survival analysis from a second stone surgery and disease associations by stone composition to validate the phenotyping method against known associations.

The NLP algorithm identified 45,235 text mentions corresponding to 11,585 patients. Overall the system achieved a positive predictive value greater than 90% for calcium oxalate monohydrate, calcium oxalate dihydrate, hydroxyapatite, brushite and struvite but not uric acid (positive predictive value 87.5%). Survival analysis from a second stone surgery showed statistically significant differences among stone types (p=0.03). Several phenotype associations were found.

From these findings the authors conclude that NLP extraction of kidney stone composition data from the large-scale EHR is feasible with high precision, enabling high throughput epidemiological studies of kidney stone disease. These tools will enable high fidelity kidney stone research from the EHR.

Krzastek SC, Sharma D, Abdullah N et al: Long-term safety and efficacy of clomiphene citrate for the treatment of hypogonadism. J Urol 2019; 202: 1029-1035.

Two common barriers to conventional testosterone normalization therapy are cost and suppression of fertility in those desiring more children. Clomiphene citrate (oral route) is inexpensive and maintains sperm count, but long-term safety data have been lacking.

The authors assessed improvements in testosterone and hypogonadal symptoms with use of clomiphene citrate for extended periods. They performed a retrospective review to identify patients treated with clomiphene citrate for hypogonadism (baseline testosterone less than 300 ng/dl) at 2 institutions from 2010 to 2018. They assessed the duration of clomiphene citrate therapy, serum testosterone levels, symptom improvement and clomiphene citrate side effects.

A total of 400 patients underwent clomiphene citrate treatment for a mean ± SD of 25.5 ± 20.48 months (range 0 to 84). Of these patients 280 received clomiphene citrate for 3 years or fewer (mean 12.75 ± 9.52 months) and 120 received it for more than 3 years (mean 51.93 ± 10.52 months). Of the men on clomiphene citrate for more than 3 years 88% achieved eugonadism, 77% reported improved symptoms and 8% reported side effects. Estradiol was significantly increased following clomiphene citrate treatment.

Results did not differ significantly between patients treated for more than 3 or 3 or fewer years. The most common side effects reported by patients treated for more than 3 years included changes in mood in 5, blurred vision in 3 and breast tenderness in 2. There was no significant adverse event in any patient treated with clomiphene citrate. The authors conclude that clomiphene citrate is safe and effective with few side effects when used as long-term treatment of hypogonadism.

Cardona-Grau D, Bush RA, Le HK et al: Reducing opioid prescriptions in outpatient pediatric urological surgery. J Urol 2019; 201: 1012-1016.

Reduction of postoperative opioid use for postoperative pain control remains an ongoing goal. However, most research to date has been on adults. The authors assessed the impact of a 2-phase Plan-Do-Study-Act cycle to decrease opioid prescriptions following pediatric urological surgery.

Parents of children undergoing outpatient urological procedures were given questionnaires to assess opioid dosing and pain scores using the Parents' Postoperative Pain Measure scale. Age, procedure and opioid prescription data were recorded as well as volume of medication administered. During the first phase of data collection children received an opioid prescription for 10 doses. In the second phase opioid prescriptions were reduced by 50%. Of 250 eligible children 98 (39%) participated and median age was 3 years.

For the 81 patients prescribed opioids a median of 2 doses (IQR 3.6) was used in the preintervention and postintervention groups (p=0.68). Using nonparametric statistical testing no significant differences were found between pain scores in the 5-dose group (31 patients) and the 10-dose group (24 patients; p=0.05 for day 1, p=0.07 for day 2, p=0.06 for day 3). There was no association between age and percent opioid used (p=0.83). There were no significant differences in median pain scores or median doses among procedure types.

The authors conclude that outpatient pediatric surgical practice opioid prescriptions can be decreased without increasing pain scores. Physician prescribing practices may contribute more to opioid consumption than actual pain patterns. ◆

AUA RESIDENTS & FELLOWS *Committee News*

Trainee Engagement in Health Policy: Organized Medicine Unifies Our Voice

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Residency serves as the most formative experience in one's professional development. During urological training one must acquire diagnostic as well as technical skills. Although a time for intense knowledge and skill acquisition, residencies across specialties fail to provide trainees with all the skills required to practice medicine today and in the future.

In an ever fluid health care environment our livelihood depends on understanding payment models, delivery systems and quality metrics. Yet pragmatic perspectives of medical practice are often neglected in surgical residencies. Medicine and policy are inevitably intertwined, but many fail to recognize this fact to the detriment of trainees, patients and the field as a whole.

Trainees often ask how they can take an active role within the sphere of health policy keeping in mind the realities of surgical training. Resident involvement in organized medicine is a practical, manageable and rewarding way to advocate for our patients and profession. There are 535 members of Congress, yet only 17 are physicians. Therefore, in order to engage the appropriate stakeholders when considering health care related policy, Congress turns to organized medicine.

The American Medical Association (AMA), the largest national association of doctors, serves as the voice of the house of medicine. The AMA meets twice a year to discuss, debate and vote on policy. The Interim Meeting of the AMA House of Delegates took place in November 2019 in San Diego, and the various sections of the AMA also held their meetings during this time. The Resident & Fellow Section provides a forum to address issues that specifically impact trainees.

This year the Resident & Fellow Section tackled several timely and important issues including minimum standards for parental leave during training, evidence-based strategies for burnout prevention and e-cigarette associated illness prevention. However, the spotlight was on the sudden, tragic closure of Hahnemann Hospital in Philadelphia, displacing 500 residents and fellows without the protection of the Accreditation Council for Graduate Medical Education. Furthermore, these trainees were left without malpractice insurance tail coverage, a potentially devastating financial situation.

The AMA voted to adopt policy to ensure financial and professional protection in the event of teaching hospital closures and assist these residents in securing tail coverage. Most importantly the policy calls for a partnership with the Centers for Medicare and Medicaid Services to establish a set of procedures and regulations to protect residents and fellows in the event of training program closures so that trainees are not left with a high degree of uncertainty, financial burden or the threat of unemployment should a similar situation arise in the future.

Doctors are quick to share their gripes regarding the authoritative administrators who receive higher salaries yet understand so little about the intricacies of patient care. These voices are rampant within the microenvironment of the physicians' lounge or hospital cafeteria. However, they must be unified to reach our policy-making bodies. Organized medicine is our forum where the rural urologist stands tall upon the shoulders of a million physicians within the U.S. There is strength in numbers but the onus falls on us to ensure our voice is heard. ◆

For more information on involvement with the AUA Health Policy Resident Workgroup, the AMA or the AUA Advocacy Summit, contact the author at ruchika.talwar@pennmedicine.upenn.edu.

FROM THE *AUA Public Policy Council*

The Value of the Patient Voice

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When we are advocating for the specialty of urology it is imperative that we remember the important role of patients in the work we do. We would not be physicians if we did not have patients. The AUA has taken a number of steps in recent years to ensure that we are able to incorporate those important voices into our advocacy efforts.

In 2016 the AUA formally integrated patient and research advocacy efforts with our legislative, state and payment advocacy activities. The Patient & Research Advocacy team continues to expand outreach to physician, research and patient advocacy partners by conducting individualized meetings with advocacy partners to establish where advocacy priorities align and identify ways to collaborate on efforts to improve patient care and access to medical treatment.

The AUA values coalition work as an effective way to strengthen our voice in the advocacy community. For the last 6 years the AUA has led the BHA (Bladder Health Alliance) with the aim of raising awareness about conditions impacting bladder health and working to remove the stigma associated with these conditions.

This year the AUA is energized to launch a new coalition called "Friends of the Prostate Cancer Care Community." The coalition will model the framework of the BHA by including all stakeholders in the prostate cancer care community including physicians, researchers and patients. The first stakeholder meeting will take place in August 2020 where the group will formalize goals and initiatives and make plans to collaboratively promote prostate cancer diagnosis, care and research in September.

Moving forward we have also added a Patient Advocacy Liaison to the Public Policy Council. Last month John Fortin officially began his role as a nonvoting member on the council. The addition of a patient advocate on the Public Policy Council will ensure patient considerations are incorporated into the planning of AUA public policy and advocacy initiatives. Mr. Fortin will provide suggestions for making advocacy efforts patient centered and considering patient implications to health policy matters. Additionally, he will serve as a resource for conveying emerging advocacy issues in the patient advocacy sector.

The AUA Annual Urology Advocacy Summit has included patient advocacy since its inception in 2018 and continues to grow each year in scope through the number of attendees, agenda topics and discussions. An integral part of the summit's growth is the inclusion of patients and patient advocates to provide insight and perspective in formulating agenda topics and participating in program areas. The 2020 AUA Summit is incorporating more than 10 patient advocates into the program planning, with additional advocates in meetings with Congressional offices and attending networking events.

Last October our BHA Roundtable meeting brought together more than 25 patient, physician and research advocacy organizations. Advocates convened for a full day to discuss topics including innovative bladder health research programs at the National Institutes of Health, collaboration opportunities for promoting policies that reduce stigma associated with bladder health conditions, how advocates can become involved with PCORI (Patient-Centered Outcomes Research Institute), the current federal research funding landscape and how advocates can best engage with lawmakers to protect funds for urological research.

The program also included a panel that drew on the expertise and insight of AUA's lobbying firm, District Policy Group, which put together an impressive panel featuring former Congressman Phil Gingrey, MD, and Senate Health and Human Services Appropriations staffer Laura Friedel. This panel discussion resulted in engaging conversation that provided attendees with tangible tactics they can use to strengthen their grassroots advocacy efforts. We look forward to another productive BHA Roundtable this year.

In summary, we do not just work with patients in our advocacy efforts, we work for them. For example, this month the AUA will discuss a change in the CPT code 54532 hypospadias repair descriptor from the term "cripple" (and "crippling") to "complication(s)" at the American Medical Association CPT Editorial Panel meeting. This effort follows a communication from a patient to AUA President John Lynch regarding the terminology used in the descriptor for CPT 54532. The patient shared his feeling that describing a patient's condition as "crippling" was demeaning and outdated. Our Coding and Reimbursement Committee agreed and the AUA has submitted a code change application.

Creating synergy between physicians and patients in the advocacy arena is an important goal for the AUA as we work to advance urology through advocacy. To learn more about our advocacy work, visit the AUAPAC booth at the AUA Annual Meeting or visit www.AUAnet.org/advocacy. ◆

Erleada® (apalutamide) 60 mg tablets

Start early with ERLEADA®

For your patients with metastatic prostate cancer who will be starting ADT or have recently initiated ADT*

NEW INDICATION

Now approved for the treatment of patients with metastatic castration-sensitive prostate cancer (mCSPC).

In the TITAN study† in patients with mCSPC:

ERLEADA® + ADT reduced the risk of death by 33% vs placebo + ADT[1]

(Median overall survival was not estimable in either arm; HR=0.67; 95% CI: 0.51, 0.89; *P*=0.0053)

INDICATION

ERLEADA® (apalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with:

- Metastatic castration-sensitive prostate cancer (mCSPC)
- Non-metastatic castration-resistant prostate cancer (nmCRPC)

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Ischemic Cardiovascular Events—In a randomized study (SPARTAN) of patients with nmCRPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA® and 3% of patients treated with placebo. In a randomized study (TITAN) in patients with mCSPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA® and 2% of patients treated with placebo. Across the SPARTAN and TITAN studies, 6 patients (0.5%) treated with ERLEADA® and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event. Patients with current evidence of unstable angina, myocardial infarction, or congestive heart failure within 6 months of randomization were excluded from the SPARTAN and TITAN studies.

Ischemic cardiovascular events, including events leading to death, occurred in patients receiving ERLEADA®. Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of ERLEADA® for Grade 3 and 4 events.

Fractures—In a randomized study (SPARTAN) of patients with nmCRPC, fractures occurred in 12% of patients treated with ERLEADA® and in 7% of patients treated with placebo. In a randomized study (TITAN) of patients with mCSPC, fractures occurred in 9% of patients treated with ERLEADA® and in 6% of patients treated with placebo. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

Falls—In a randomized study (SPARTAN), falls occurred in 16% of patients treated with ERLEADA® compared with 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Falls occurred in patients receiving ERLEADA® with increased frequency in the elderly. Evaluate patients for fall risk.

Seizure—In 2 randomized studies (SPARTAN and TITAN), 5 patients (0.4%) treated with ERLEADA® and 1 patient treated with placebo (0.1%) experienced a seizure. Permanently discontinue ERLEADA® in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA®. Advise patients of the risk of developing a seizure while receiving ERLEADA® and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

Embryo-Fetal Toxicity—The safety and efficacy of ERLEADA® have not been established in females. Based on its mechanism of action, ERLEADA® 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 and for 3 months after the last dose of ERLEADA® *[see Use in Specific Populations (8.1, 8.3)]*.

ADVERSE REACTIONS

Adverse Reactions—The most common adverse reactions (≥10%) that occurred more frequently in the ERLEADA®-treated patients (≥2% over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea, and fracture.

Laboratory Abnormalities—All Grades (Grade 3-4)

- **Hematology**—In the TITAN study: white blood cell decreased ERLEADA® 27% (0.4%), placebo 19% (0.6%). In the SPARTAN study: anemia ERLEADA® 70% (0.4%), placebo 64% (0.5%); leukopenia ERLEADA® 47% (0.3%), placebo 29% (0%); lymphopenia ERLEADA® 41% (2%), placebo 21% (2%)
- **Chemistry**—In the TITAN study: hypertriglyceridemia ERLEADA® 17% (3%), placebo 12% (2%). In the SPARTAN study: hypercholesterolemia ERLEADA® 76% (0.1%), placebo 46% (0%); hyperglycemia ERLEADA® 70% (2%), placebo 59% (1%); hypertriglyceridemia ERLEADA® 67% (2%), placebo 49% (0.8%); hyperkalemia ERLEADA® 32% (2%), placebo 22% (0.5%)

Rash—In 2 randomized studies, rash was most commonly described as macular or maculopapular. Adverse reactions of rash were 26% with ERLEADA® vs 8% with placebo. Grade 3 rashes (defined as covering >30% body surface area [BSA]) were reported with ERLEADA® treatment (6%) vs placebo (0.5%).

The onset of rash occurred at a median of 83 days. Rash resolved in 78% of patients within a median of 78 days from onset of rash. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 28% of patients, respectively. Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of ERLEADA®.

Hypothyroidism—In 2 randomized studies, hypothyroidism was reported for 8% of patients treated with ERLEADA® and 2% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA® and 7% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted.

DRUG INTERACTIONS

Effect of Other Drugs on ERLEADA®—Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties. No initial dose adjustment is necessary; however, reduce the ERLEADA® dose based on tolerability *[see Dosage and Administration (2.2)]*.

Effect of ERLEADA® on Other Drugs—ERLEADA® is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA® with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA® with medications that are substrates of UDP-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA® and evaluate for loss of activity.

P-gp, BCRP, or OATP1B1 Substrates—Apalutamide is a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. Concomitant use of ERLEADA® with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP, or OATP1B1 must be co-administered with ERLEADA® and evaluate for loss of activity if medication is continued.

Please see Brief Summary of full Prescribing Information for ERLEADA® on subsequent pages.

*All patients who enrolled in the TITAN study started ADT for mCSPC ≤6 months prior to randomization.

†**Study Design:** TITAN was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of patients with mCSPC (N=1052). Patients had *de novo* mCSPC or relapsed metastatic disease after initial diagnosis of localized disease. All patients in the TITAN trial received a concomitant GnRH analog or had a bilateral orchiectomy. Patients with visceral (ie, liver or lung) metastases as the only sites of metastases were excluded. Patients were randomized 1:1 to receive ERLEADA® 240 mg orally once daily + ADT or placebo orally once daily + ADT. The dual primary endpoints were overall survival and radiographic progression-free survival.[1,2]

References: 1. ERLEADA® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Chi KN, Agarwal N, Bjartell A, et al; on behalf of TITAN investigators. Apalutamide for metastatic castration-sensitive prostate cancer. *N Engl J Med*. In press.

ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; TITAN = Targeted Investigational Treatment Analysis of Novel Antiandrogen.

Janssen Biotech, Inc.

Janssen Oncology

PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Erleada® (apalutamide) 60 mg tablets

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cp-50507-cp

Brief Summary of Prescribing Information for ERLEADA® (apalutamide)

ERLEADA® (apalutamide) tablets, for oral use

See package insert for Full Prescribing Information

INDICATIONS AND USAGE

ERLEADA is indicated for the treatment of patients with

- Metastatic castration-sensitive prostate cancer (mCSPC)
- Non-metastatic castration-resistant prostate cancer (nmCRPC)

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Ischemic Cardiovascular Events

Ischemic cardiovascular events, including events leading to death, occurred in patients receiving ERLEADA. Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of ERLEADA for Grade 3 and 4 events.

In a randomized study (SPARTAN) of patients with nmCRPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA and 3% of patients treated with placebo. In a randomized study (TITAN) in patients with mCSPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA and 2% of patients treated with placebo. Across the SPARTAN and TITAN studies, 6 patients (0.5%) treated with ERLEADA and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event. Patients with current evidence of unstable angina, myocardial infarction, or congestive heart failure within six months of randomization were excluded from the SPARTAN and TITAN studies.

Fractures

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

In a randomized study (SPARTAN) of patients with non-metastatic castration-resistant prostate cancer, fractures occurred in 12% of patients treated with ERLEADA and in 7% of patients treated with placebo. Grade 3-4 fractures occurred in 3% of patients treated with ERLEADA and in 1% of patients treated with placebo. The median time to onset of fracture was 314 days (range: 20 to 953 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the SPARTAN study.

In a randomized study (TITAN) of patients with metastatic castration-sensitive prostate cancer, fractures occurred in 9% of patients treated with ERLEADA and in 6% of patients treated with placebo. Grade 3-4 fractures were similar in both arms at 2%. The median time to onset of fracture was 56 days (range: 2 to 111 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the TITAN study.

Falls

Falls occurred in patients receiving ERLEADA with increased frequency in the elderly *[See Use in Specific Populations]*. Evaluate patients for fall risk.

In a randomized study (SPARTAN), falls occurred in 16% of patients treated with ERLEADA compared to 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure.

Seizure

Seizure occurred in patients receiving ERLEADA. Permanently discontinue ERLEADA in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA. Advise patients of the risk of developing a seizure while receiving ERLEADA and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

In two randomized studies (SPARTAN and TITAN), five patients (0.4%) treated with ERLEADA and one patient treated with placebo (0.1%) experienced a seizure. Seizure occurred from 159 to 650 days after initiation of ERLEADA. Patients with a history of seizure, predisposing factors for seizure, or receiving drugs known to decrease the seizure threshold or to induce seizure were excluded. There is no clinical experience in re-administering ERLEADA to patients who experienced a seizure.

Embryo-Fetal Toxicity

The safety and efficacy of ERLEADA have not been established in females. Based on its mechanism of action, ERLEADA can cause fetal harm and loss of pregnancy when administered to a pregnant female *[see Clinical Pharmacology (12.1) in full Prescribing Information]*. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA *[see Use in Specific Populations]*.

ADVERSE REACTIONS

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

- Ischemic Cardiovascular Events *[see Warnings and Precautions]*.
- Fractures *[see Warnings and Precautions]*.
- Falls *[see Warnings and Precautions]*.
- Seizure *[see Warnings and Precautions]*.

Clinical Trial Experience

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

The most common adverse reactions (≥ 10%) that occurred more frequently in the ERLEADA-treated patients (≥ 2% over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea, and fracture.

Metastatic Castration-sensitive Prostate Cancer (mCSPC)

TITAN, a randomized (1:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had mCSPC. In this study, patients received either ERLEADA at a dose of 240 mg daily or placebo. All patients in the TITAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had prior bilateral orchiectomy. The median duration of exposure was 20 months (range: 0 to 34 months) in patients who received ERLEADA and 18 months (range: 0.1 to 34 months) in patients who received placebo.

Ten patients (2%) who were treated with ERLEADA died from adverse reactions. The reasons for death were ischemic cardiovascular events (n=3), acute kidney injury (n=2), cardio-respiratory arrest (n=1), sudden cardiac death (n=1), respiratory failure (n=1), cerebrovascular accident (n=1), and large intestinal ulcer perforation (n=1). ERLEADA was discontinued due to adverse reactions in 8% of patients, most commonly from rash (2%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 23% of patients; the most frequent (>1%) were rash, fatigue, and hypertension. Serious adverse reactions occurred in 20% of ERLEADA-treated patients and 20% in patients receiving placebo.

Table 1 shows adverse reactions occurring in ≥10% on the ERLEADA arm in TITAN that occurred with a ≥2% absolute increase in frequency compared to placebo. Table 2 shows laboratory abnormalities that occurred in ≥15% of patients, and more frequently (>5%) in the ERLEADA arm compared to placebo.

Table 1: Adverse Reactions in TITAN (mCSPC)

	ERLEADA N=524		Placebo N=527	
System/Organ Class Adverse reaction	**All Grades %**	**Grade 3-4 %**	**All Grades %**	**Grade 3-4 %**
General disorders and administration site conditions				
Fatigue[1,3]	26	3	25	2
Musculoskeletal and connective tissue disorders				
Arthralgia[3]	17	0.4	15	0.9
Skin and subcutaneous tissue disorders				
Rash[2]	28	6	9	0.6
Pruritus	11	<1	5	<1
Vascular disorders				
Hot flush	23	0	16	0
Hypertension	18	8	16	9

[1] Includes fatigue and asthenia

[2] Includes rash, rash maculo-papular, rash generalized, urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash papular, skin exfoliation, genital rash, rash erythematous, stomatitis, drug eruption, mouth ulceration, rash pustular, blister, papule, pemphigoid, skin erosion, dermatitis, and rash vesicular

[3] Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3

Additional adverse reactions of interest occurring in 2%, but less than 10% of patients treated with ERLEADA included diarrhea (9% versus 6% on placebo), muscle spasm (3% versus 2% on placebo), dysgeusia (3% versus 1% on placebo), and hypothyroidism (4% versus 1% on placebo).

Table 2: Laboratory Abnormalities Occurring in ≥ 15% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference > 5% All Grades) in TITAN (mCSPC)

	ERLEADA N=524		Placebo N=527	
Laboratory Abnormality	**All Grades %**	**Grade 3-4 %**	**All Grades %**	**Grade 3-4 %**
Hematology				
White blood cell decreased	27	0.4	19	0.6
Chemistry				
Hypertriglyceridemia[1]	17	3	12	2

[1] Does not reflect fasting values

Non-metastatic Castration-resistant Prostate Cancer (nmCRPC)

SPARTAN, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had nmCRPC. In this study, patients received either ERLEADA at a dose of 240 mg daily or a placebo. All patients in the SPARTAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. The median duration of exposure was 16.9 months (range: 0.1 to 42 months) in patients who received ERLEADA and 11.2 months (range: 0.1 to 37 months) in patients who received placebo.

Eight patients (1%) who were treated with ERLEADA died from adverse reactions. The reasons for death were infection (n=4), myocardial infarction (n=3), and cerebral hemorrhage (n=1). One patient (0.3%) treated with placebo died from an adverse reaction of cardiopulmonary arrest (n=1). ERLEADA was discontinued due to adverse reactions in 11% of patients, most commonly from rash (3%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 33% of patients; the most common (>1%) were rash, diarrhea, fatigue, nausea, vomiting, hypertension, and hematuria. Serious adverse reactions occurred in 25% of ERLEADA-treated patients and 23% in patients receiving placebo. The most frequent serious adverse reactions (>2%) were fracture (3%) in the ERLEADA arm and urinary retention (4%) in the placebo arm.

Table 3 shows adverse reactions occurring in ≥10% on the ERLEADA arm in SPARTAN that occurred with a ≥2% absolute increase in frequency compared to placebo. Table 4 shows laboratory abnormalities that occurred in ≥15% of patients, and more frequently (>5%) in the ERLEADA arm compared to placebo.

Table 3: Adverse Reactions in SPARTAN (nmCRPC)

	ERLEADA N=803		Placebo N=398	
System/Organ Class Adverse reaction	**All Grades %**	**Grade 3-4 %**	**All Grades %**	**Grade 3-4 %**
General disorders and administration site conditions				
Fatigue[1,4]	39	1	28	0.3
Musculoskeletal and connective tissue disorders				
Arthralgia[4]	16	0	8	0
Skin and subcutaneous tissue disorders				
Rash[2]	25	5	6	0.3

Table 3: Adverse Reactions in SPARTAN (nmCRPC) (continued)

	ERLEADA N=803		Placebo N=398	
System/Organ Class Adverse reaction	**All Grades %**	**Grade 3-4 %**	**All Grades %**	**Grade 3-4 %**
Metabolism and nutrition disorders				
Decreased appetite[5]	12	0.1	9	0
Peripheral edema[6]	11	0	9	0
Injury, poisoning and procedural complications				
Fall[4]	16	2	9	0.8
Fracture[3]	12	3	7	0.8
Investigations				
Weight decreased[4]	16	1	6	0.3
Vascular disorders				
Hypertension	25	14	20	12
Hot flush	14	0	9	0
Gastrointestinal disorders				
Diarrhea	20	1	15	0.5
Nausea	18	0	16	0

[1] Includes fatigue and asthenia

[2] Includes rash, rash maculo-papular, rash generalized, urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash papular, skin exfoliation, genital rash, rash erythematous, stomatitis, drug eruption, mouth ulceration, rash pustular, blister, papule, pemphigoid, skin erosion, dermatitis, and rash vesicular

[3] Includes rib fracture, lumbar vertebral fracture, spinal compression fracture, spinal fracture, foot fracture, hip fracture, humerus fracture, thoracic vertebral fracture, upper limb fracture, fractured sacrum, hand fracture, pubis fracture, acetabulum fracture, ankle fracture, compression fracture, costal cartilage fracture, facial bones fracture, lower limb fracture, osteoporotic fracture, wrist fracture, avulsion fracture, fibula fracture, fractured coccyx, pelvic fracture, radius fracture, sternal fracture, stress fracture, traumatic fracture, cervical vertebral fracture, femoral neck fracture, and tibia fracture

[4] Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3

[5] Includes appetite disorder, decreased appetite, early satiety, and hypophagia

[6] Includes peripheral edema, generalized edema, edema, edema genital, penile edema, peripheral swelling, scrotal edema, lymphedema, swelling, and localized edema

Additional clinically significant adverse reactions occurring in 2% or more of patients treated with ERLEADA included hypothyroidism (8.1% versus 2% on placebo), pruritus (6.2% versus 2% on placebo), and heart failure (2.2% versus 1% on placebo).

Table 4: Laboratory Abnormalities Occurring in ≥ 15% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference > 5% All Grades) in SPARTAN (nmCRPC)

	ERLEADA N=803		Placebo N=398	
Laboratory Abnormality	**All Grades %**	**Grade 3-4 %**	**All Grades %**	**Grade 3-4 %**
Hematology				
Anemia	70	0.4	64	0.5
Leukopenia	47	0.3	29	0
Lymphopenia	41	2	21	2
Chemistry				
Hypercholesterolemia[1]	76	0.1	46	0
Hyperglycemia[1]	70	2	59	1
Hypertriglyceridemia[1]	67	2	49	0.8
Hyperkalemia	32	2	22	0.5

[1] Does not reflect fasting values

Rash

In the combined data of two randomized, placebo-controlled clinical studies, rash associated with ERLEADA was most commonly described as macular or maculo-papular. Adverse reactions of rash were reported for 26% of patients treated with ERLEADA versus 8% of patients treated with placebo. Grade 3 rashes (defined as covering > 30% body surface area [BSA]) were reported with ERLEADA treatment (6%) versus placebo (0.5%).

The onset of rash occurred at a median of 83 days of ERLEADA treatment. Rash resolved in 78% of patients within a median of 78 days from onset of rash. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 28% of patients, respectively. Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of ERLEADA.

Hypothyroidism

In the combined data of two randomized, placebo-controlled clinical studies, hypothyroidism was reported for 8% of patients treated with ERLEADA and 2% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA and 7% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy was initiated in 5% of patients treated with ERLEADA. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted *[see Drug Interactions]*.

DRUG INTERACTIONS

Effect of Other Drugs on ERLEADA

Strong CYP2C8 or CYP3A4 Inhibitors

Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties (sum of unbound apalutamide plus the potency-adjusted unbound N-desmethyl-apalutamide). No initial dose adjustment is necessary however, reduce

the ERLEADA dose based on tolerability *[see Dosage and Administration (2.2) in full Prescribing Information].* Mild or moderate inhibitors of CYP2C8 or CYP3A4 are not expected to affect the exposure of apalutamide.

Effect of ERLEADA on Other Drugs

CYP3A4, CYP2C9, CYP2C19 and UGT Substrates

ERLEADA is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA with medications that are substrates of UDP-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA and evaluate for loss of activity *[see Clinical Pharmacology (12.3) in full Prescribing Information].*

P-gp, BCRP or OATP1B1 Substrates

Apalutamide was shown to be a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. At steady-state, apalutamide reduced the plasma exposure to fexofenadine (a P-gp substrate) and rosuvastatin (a BCRP/OATP1B1 substrate). Concomitant use of ERLEADA with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP or OATP1B1 must be co-administered with ERLEADA and evaluate for loss of activity if medication is continued *[see Clinical Pharmacology (12.3) in full Prescribing Information].*

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

The safety and efficacy of ERLEADA have not been established in females. Based on its mechanism of action, ERLEADA can cause fetal harm and loss of pregnancy *[see Clinical Pharmacology (12.1) in full Prescribing Information]*. There are no human data on the use of ERLEADA in pregnant women. ERLEADA is not indicated for use in females, so animal embryo-fetal developmental toxicology studies were not conducted with apalutamide.

Lactation

Risk Summary

The safety and efficacy of ERLEADA have not been established in females. There are no data on the presence of apalutamide or its metabolites in human milk, the effect on the breastfed child, or the effect on milk production.

Females and Males of Reproductive Potential

Contraception

Males

Based on the mechanism of action and findings in an animal reproduction study, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA. *[see Use in Specific Populations].*

Infertility

Males

Based on animal studies, ERLEADA may impair fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1) in full Prescribing Information].*

Pediatric Use

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

Geriatric Use

Of the 1327 patients who received ERLEADA in clinical studies, 19% of patients were less than 65 years, 41% of patients were 65 years to 74 years, and 40% were 75 years and over.

No overall differences in effectiveness were observed between older and younger patients.

Of patients treated with ERLEADA (n=1073), Grade 3-4 adverse reactions occurred in 39% of patients younger than 65 years, 41% of patients 65-74 years, and 49% of patients 75 years or older. Falls in patients receiving ERLEADA with androgen deprivation therapy was elevated in the elderly, occurring in 8% of patients younger than 65 years, 10% of patients 65-74 years, and 19% of patients 75 years or older.

OVERDOSAGE

There is no known specific antidote for apalutamide overdose. In the event of an overdose, stop ERLEADA, undertake general supportive measures until clinical toxicity has been diminished or resolved.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Ischemic Cardiovascular Events

- Inform patients that ERLEADA has been associated with ischemic cardiovascular events. Advise patients to seek immediate medical attention if any symptoms suggestive of a cardiovascular event occur *[see Warnings and Precautions]*.

Falls and Fractures

- Inform patients that ERLEADA is associated with an increased incidence of falls and fractures *[see Warnings and Precautions].*

Seizures

- Inform patients that ERLEADA has been associated with an increased risk of seizure. Discuss conditions that may predispose to seizures and medications that may lower the seizure threshold. Advise patients of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Inform patients to contact their healthcare provider right away if they experience a seizure *[see Warnings and Precautions].*

Rash

- Inform patients that ERLEADA is associated with rashes and to inform their healthcare provider if they develop a rash *[see Adverse Reactions].*

Dosage and Administration

- Inform patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with ERLEADA.
- Instruct patients to take their dose at the same time each day (once daily). ERLEADA can be taken with or without food. Each tablet should be swallowed whole.
- Inform patients that in the event of a missed daily dose of ERLEADA, they should take their normal dose as soon as possible on the same day with a return to the normal schedule on the following day. The patient should not take extra tablets to make up the missed dose *[see Dosage and Administration (2.1) in full Prescribing Information].*

Embryo-Fetal Toxicity

- Inform patients that ERLEADA can be harmful to a developing fetus. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA. Advise male patients to use a condom if having sex with a pregnant woman *[see Warnings and Precautions].*

Infertility

- Advise male patients that ERLEADA may impair fertility and not to donate sperm during therapy and for 3 months following the last dose of ERLEADA *[see Use in Specific Populations].*

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Janssen Ortho LLC
Gurabo, PR 00778

Manufactured for:
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cp-50510v2

FROM THE *AUA Secretary*

Wrapping our Specialty around the World

John D. Denstedt, MD, FRCSC, FACS, FCAHS
Editor, AUA*News*
London, Ontario, Canada

When someone mentions globalization, we think of the growing interdependencies of cultures, populations and economies. Many may also envision the interconnection of countries, giving way to an exchange of information as well as free trade of goods, services and technologies. However when we talk about globalization of health care, do we envision the same interdependency and interconnection? For some, their vision includes the faster spread of disease due to an increase in global travel, while others think about rapid response times to epidemics and catastrophes, and saving thousands of lives.

With more than 23,000 members worldwide, AUA is committed to globalization of health care through the development of widespread collaborations with our global partners. These collaborations involve promoting the interchange of urological skills, fostering research and discovery, and developing educational resources to benefit the urology community.

The world of medicine is no longer bound by the constraints of international borders, and technology makes it easier than ever to reach providers and patients, and manage disease and care. From a supply chain perspective, even if you consider yourself working for a "domestic" company, it is likely you are dependent on equipment and materials produced from other regions of the world. At its best, health care globalization brings partners together to create comprehensive solutions. It changes people's lives, expands hope and opens opportunities.

As the official foundation of the AUA, the Urology Care Foundation continues to grow as the world's single largest repository for medically approved urological patient education. Presently, the Foundation offers more than 300 patient education materials on urological conditions affecting children as well as male and female geriatric patients. Through a partnership with the Confederación Americana de Urología (CAU) and Société Internationale d'Urologie, many of the popular patient education resources are translated into Spanish and Italian. In addition, translated materials are also available in Brazilian Portuguese and Punjabi languages. Having these resources available in various languages makes this important information available to patients worldwide.

Today, the AUA has projects to advance and support the globalization of health care in more than 100 countries on 6 continents. We are currently working with CAU on the Spanish translation of 13 clinical practice guidelines as well as our Guidelines-At-A-Glance pocket guide. In conjunction with the Canadian Urological Association we are translating our recurrent urinary tract infection clinical guideline into French Canadian, and the guideline pocket guide will be translated into Brazilian Portuguese through a partnership with Sociedad Brasileira de Urologia.

In addition, we publish translated editions of *The Journal of Urology®*, the official journal of the AUA, for our members in Japan and India, and AUA*News*, the official newsmagazine of the AUA, for our members in Spain, India and Portugal.

In 2019 we conducted educational programs in Argentina, Bangladesh, Brazil, Canada, Chile, Colombia, Egypt, India, Italy, Kuwait, Mexico, Peru, Saudi Arabia, South Korea and Turkey. We also collaborated with societies around the world to hold endourology courses and hands-on training workshops. This year we hope to expand our international programs to more countries.

The AUA also oversees academic exchange programs for junior faculty and residents. These funded fellowship programs encourage the interchange of urological skills, expertise and knowledge, which are critical to the continued success of urology worldwide. Last year 17 urologists from Brazil, Germany, Greece, India, Italy, Japan, Mexico, the United Kingdom and the United States participated in our exchange and visiting scholar programs. In 2020 China will be added to this list.

The demand for globalization of health care continues today and by facilitating the exchange of information and perspectives on clinical practice and patient care, the AUA is promoting strong dialogue, bolstering collaborations, and helping our specialty grow and advance.◆

FROM THE *Urology Care Foundation*

Supporting Science and the Scientist

Harris M. Nagler, MD, FACS
President, Urology Care Foundation
New York, New York

As physicians, science is at the very foundation of what we do. Advancements—from the earliest understanding of the basic biology of a disease to the development of new treatments and prevention methods in urological care—would not exist without research. Supporting research and the scientists who are committed to discoveries and finding breakthroughs is a key pillar of the mission of the Urology Care Foundation.

Since 1975 the Foundation has funded more than $30 million in research. We understand how important it is to not only support science, but also the scientist, especially as funding cuts and increased competition for federal grants continue to threaten the future of urological research.

In the last 2 decades the Foundation has expanded its portfolio of mentored training awards aimed at recruiting into research young urologists and scientists, and providing them with the critical assistance necessary to become our next rising stars and research leaders. We are committed to ensuring that awardees are supported so that they may thrive in today's ever-changing research environment. We offer 5 unique award mechanisms that have already benefited more than 750 young scientists at various stages of their careers, as well as a full array of educational programming centered on career development skills, such as grant writing and research plan development.

We are proud of our awardees and the programs we have developed, particularly with regard to the impact these programs are having on their careers. A recent outcomes analysis of the Foundation's Rising Stars in Urology program, an award program established in 2005, explored the impact of the program on research career longevity. We examined the full Rising Stars applicant pool for 2005 to 2014, and compared the subsequent achievements of those who received awards with those who did not.

Our analysis revealed that Rising Star award recipients earned at least 1 federally funded research grant compared to unfunded applicants, and were nearly twice as successful applying for R01 grants from the National Institutes of Health (see table). In addition, Rising Stars published more scientific articles than unfunded applicants. Finally, more than 73% of awardees reported protected time and salary support to be the greatest impact of the award on their careers. All Rising Star award recipients characterized the award as either essential or very helpful to their career development.

I encourage you to visit www.UrologyHealth.org to learn more about our research scholars and the various award programs the Foundation has to offer. Please review our new IMPACT magazine (www.AUAnet.org/IMPACT) to learn more about how our research education and funding initiatives support many investigators in their careers, and how these contributions impact patient care. You can be proud of your Foundation and its impact on scientists and patients. ◆

Table. Achievements of award versus nonaward recipients

	Rising Star Award Recipients	Nonaward Recipients
Earned federally funded grant	93%	64%
Successful R01 grant applications	61.5%	36.3%
Average No. scientific articles published	109.6	52

FROM THE *AUA Education Council*

AUA's Flexible Learning Design

Victor W. Nitti, MD
Chair, AUA Education Council
Los Angeles, California

The AUA believes in providing the best support and resources to its members. We understand you have busy schedules and need the time to take care of your patients, your family and yourself. We continue to strive to bring you learning opportunities when and how they are most beneficial for you. With that in mind, we developed a flexible learning design which customizes learning environments to meet your learning needs.

The AUA Office of Education produced the first AUA*University* podcast in 2016 and now offers more than 100 clinical episodes resulting in over 112,000 downloads in 2019. A survey of our members to learn who was listening to podcasts and why revealed that

- 49% of AUA members listen to podcasts, of whom 60% are younger than 35 years old
- 19% of AUA members listen to AUA podcasts, of whom 91% listen for new information and learning opportunities, 88% find the podcasts valuable and 82% state the podcasts offer new ideas.

A new 30 to 60-minute AUA*University* podcast is released every week for your convenience. To access the podcasts directly on the AUA*University*, go to the home page and click on an episode. You can also subscribe to the podcasts on Apple® iTunes®, Google Play™ and SoundCloud by searching for "AUAUniversity" and tapping Subscribe.

To build on the popularity of the AUA*University* podcasts, a new audiobook of the AUA Update Series was offered this year. Unlike a podcast which is always episodic and variable, an audiobook is a recording of preexisting text. This format will allow you to learn on the go and when your schedule allows. The audiobook is available with the release of the print and online versions of each lesson. If you would like to listen to a free sample of an Update Series audiobook go to https://auau.auanet.org/content/update-series-volume-39-2020#group-tabs-node-course-default1.

The AUA annual meeting will be held in Washington, DC May 15-18, 2020. We believe that if you are going to leave your practice to attend our meeting, then we must offer a variety of activities to meet your educational needs. AUA2020 will include discussions that span the field of urological topics offered in a variety of learning formats to fit your personal learning preferences. New in 2020, we will offer 6 instructional courses in an alternative format different from the typical didactic lectures. For those who want more case-based learning, we will conduct 6 courses in which 100% of the content is derived from case presentations. Alternative format and case-based instructional courses will be identified in the course descriptions. If you would like more information about this year's AUA meeting, visit www.aua2020.org.

We welcome your feedback. If you have a suggestion or recommendation that you would like to share, please email us at education@auanet.org. ◆

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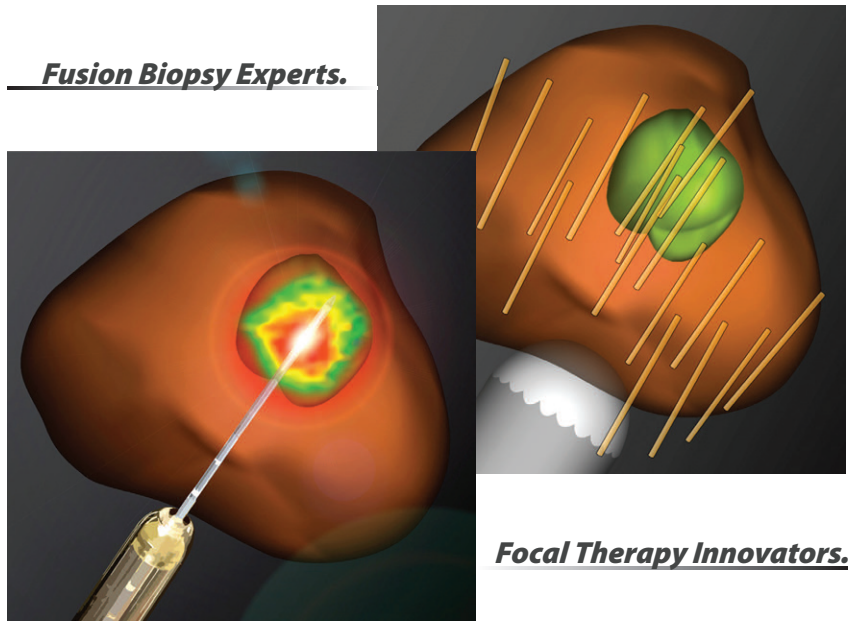

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Recent urology grads and current residents are invited to apply for a unique 1-year fellowship*. At UCLA Urology, we train thought leaders in urologic oncology in a program emphasizing contemporary management of prostate cancer.

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"My fellowship at UCLA has given me a career-launching experience with hundreds of targeted biopsies and focal therapy cases. I would do this again in a heartbeat."

-Adam Kinnaird, MD PhD FRCSC, 2019-2020 Fellow

Applications are now being accepted for July 2020
Interested applicants should directly contact:
Dr. Leonard Marks at lmarks@mednet.ucla.edu

Detailed description: http://bit.ly/urologyFellowship2020
Youtube Channel: targetedProstateBiopsy.com

**CA licensure/eligibility a pre-requisite.*

Top row: Peter Kuhn, PhD; Jeremy Mason, PhD; David Ginsberg, MD; Eric Kau, MD; Andy Chang, MD; Andrew Hung, MD; Andre Abreu, MD. **Second row:** Paul Kokorowski, MD; Peter Roffey, MD; Giovanni Cacciamani, MD; Jamal Nabhani, MD; Evgeniy Kreydin, MD; Jeff Loh-Doyle, MD; Mike Nguyen, MD. **Third row:** Monish Aron, MD; J Ko, MD; Evalynn Vasquez, MD; Anne Schuckman, MD; Roger DeFilippo, MD; Virinder Bhardwaj, MD; Mary Samplaski, MD; Leslie Ballas, MD; Rhong Zhang, PhD. **Front row:** Sia Daneshmand, MD; Rene Sotelo, MD; Gerhard Fuchs, MD; Inderbir Gill, MD; Mihir Desai, MD; Larissa Rodriguez, MD; Hooman Djaladat, MD; Gangning Liang, PhD

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