For U.S. urologists, working with nurse practitioners and physician assistants has become more the norm than the exception.

More than 70% of practicing urologists work with one or more nurse practitioners and physician assistants, collectively called advanced practice providers (APPs), according to 2017 AUA Census data. By comparison, 62.7% of urologists worked with an APP in 2015.

“A decade ago it was rare to have advanced practice providers as part of routine urologic care. Now they’re integral and a necessary part of any active urologic practice,” said Bradley A. Erickson, MD, MS, associate professor of urology and surgery, University of Iowa, Iowa City.

Urology isn’t the only specialty with a growing
What is my patient’s risk for aggressive cancer despite a negative biopsy?

ConfirmMDx for Prostate Cancer

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

The test helps you:

RULE IN those who may require repeat biopsies and potential treatment.

RULE OUT prostate cancer-free men from undergoing unnecessary repeat biopsies

ConfirmMDx Clinical Validity & Utility

- 96% NPV for GS ≥ 7 Prostate Cancer
- 90% NPV for All Prostate Cancer
- Included in the 2016 NCCN Guidelines

ConfirmMDx Provides the Likelihood of Detecting Gleason Score ≥ 7 Cancer on Repeat Biopsy

The Most Significant Independent Predictor for Prostate Cancer on Repeat Biopsy

Odds Ratio for GS ≥ 7

<table>
<thead>
<tr>
<th>N = 803</th>
<th>15.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.0</td>
</tr>
<tr>
<td>%+Biopsies</td>
<td>1.5</td>
</tr>
<tr>
<td>PSA</td>
<td>2.3</td>
</tr>
<tr>
<td>Atypia</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Clinical Risk Factors

MDxHealth is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. The ConfirmMDx for Prostate Cancer test was developed and its performance characteristics determined by MDxHealth. It has not been cleared or approved by the US Food and Drug Administration. The test results should be interpreted in conjunction with other laboratory and clinical data available to the clinician and relevant guidelines on the decision for biopsy.

REFERENCES:
BPH procedures and med use: Two sides of a coin

STEVEN A. KAPLAN, MD
Dr. Kaplan, a member of the Urology Times Editorial Council, is professor of urology at the Kiah School of Medicine at Mount Sinai, New York.

When analyzing efficacy of minimally invasive/surgical therapies for lower urinary tract symptoms secondary to BPH, we appropriately focus on subjective criteria (eg, symptom improvement and sexual adverse events) and objective criteria (eg, changes in uroflow and post-void residual urine). While we reevaluate treatment rates, we don’t measure failure of therapies by how many men restart LUTS/BPH medications. It’s an important question both in terms of economics and managing patient expectations.

Gill et al shed light on medication discontinuation after either a minimally invasive surgical therapy (MIST) or surgical therapy for BPH/LUTS (page 4). Not surprisingly, the more tissue removed, the greater likelihood of discontinuing pre-procedure drugs. Gill et al analyzed BPH procedures between 2001 and 2016 and included men who underwent laser vaporization (n=2,499), transurethral resection (2,304), microwave or needle ablation (165), and open prostaticctomy (132). At 3 months, 80.3% of MIST patients discontinued therapy versus 91.5% of laser vaporization and 98.6% of open prostatectomy patients.

Notwithstanding the differences in the number of patients in each group, this makes intuitive sense. The more tissue removed, the more likely patients will have initial success as manifested by discontinuing medications. That’s the good news. The other side of the coin is that the more tissue removed, the greater likelihood of ejaculation issues with open prostatectomy than with MIST. We convinced ourselves that this might not matter to patients. It does!

Also, while the report is valuable in helping us discern medication discontinuation rates, it did not address how many patients go back on a LUTS/BPH drug months or years after the procedure. Numerous reports show that from 33% to 50% of men may go back on medication after a BPH procedure, including TURP.

Why the high rate of restarting medications after BPH procedures? Potential factors include proper patient selection (ie, in individual men, is LUTS secondary to BPH and bladder outlet obstruction versus other non-medical factors) and varied experiences of urologists with various procedures. Moreover, do newer forms of MIST, such as Urolift and Rezum, result in different post-procedure profiles? In addition, patients and urologists may have varied thresholds for stopping and/or restarting medications.

Given the retrospective nature of the study, it’s hard to define treatment success and/or failure.

Finally, we should ask ourselves if long-term medical therapy for what is essentially a quality of life disorder is reasonable. Data are evolving about the potential role of long-term alpha-blocker and finasteride use in dementia. Should we be advocating medical therapy given the improvement of MIST and surgical therapies for BPH? Thought processes are evolving, and urologists need to take the lead as the recognized experts in managing LUTS secondary to BPH.
Clinical Updates

BPH / Tissue-eliminating techniques outperform tissue-necrosing methods

Which BPH procedures best reduce need for medication?

Laird Harrison
UT Correspondent

SAN FRANCISCO—Tissue-eliminating procedures outperform tissue-necrosing procedures for reducing the need for medication in patients with benign prostatic enlargement (BPE), researchers say.

“There’s less advantage to heating the tissue,” Bradley Gill, MD, chief urology resident at Cleveland Clinic, told Urology Times. Dr. Gill, working with Daniel Shoskes, MD, and colleagues, presented the findings at the AUA annual meeting in San Francisco.

Medical treatments for BPE don’t always work, may be expensive, and cause adverse effects, he said. But few studies have examined the effectiveness of surgery in reducing the need for medication.

Dr. Gill and his colleagues hypothesized that tissue-eliminating procedures would beat tissue-necrosing procedures at allowing patients to avoid urologic medication.

To see if they were right, they analyzed records of BPE procedures from 2001 to 2016 at Cleveland Clinic. The researchers included 2,549 patients who underwent photovaporization, 2,304 who underwent transurethral resection, 165 who underwent simple prostatectomy, and 132 who underwent simple prostatectomy.

They defined a medication as discontinued if it was used before surgery but not from 3 months afterward. A medication was defined as resumed if the patient started using it again after discontinuing it. And a medication was defined as initiated if it was used from 3 months after but not before surgery.

Grouped by procedure, the patients’ demographics were similar, but there were some statistically significant differences. The most significant was that only 37% of those undergoing microwave or needle ablation (which the authors lumped together in analyses) were using 5-alpha-reductase inhibitors at baseline, compared to 44.4% of those undergoing photovaporization, 51.8% of those undergoing transurethral resection, and 53.8% of those undergoing simple prostatectomy ($p < .01$).

There were differences in baseline alpha-blocker use as well; this class of drugs was used by 68.2% of the simple prostatectomy group, 79.6% of the transurethral resection group, 79.7% of the photovaporization group, and 83.6% of the microwave/needle ablation group.

In addition, only 15.8% of the simple prostatectomy group had coronary artery disease, compared to 18.8% of the microwave/needle ablation group, 25.7% of the transurethral resection group, and 25.9% of the photovaporization group.

There were less significant differences in baseline anticholinergic drug use, history of smoking, age at surgery, and baseline beta-3 agonist use. Differences in alcohol abuse and type 2 diabetes were not statistically significant.

### Simple prostatectomy patients stop 5-ARIs

Three months after the procedures, the authors found that 98.6% of simple prostatectomy patients were able to discontinue use of 5-alpha-reductase inhibitors, compared to 91.5% of photovaporization patients, 89.4% of transurethral resection patients, and 80.3% of microwave or needle ablation patients. The differences were statistically significant ($p < .01$). Differences in initiation of these drugs were not significant.

Similarly, 95.6% of the simple prostatectomy patients, 90.2% of the photovaporization patients, 89.1% of the transurethral resection patients, and 78.3% of the microwave or needle ablation patients stopped using alpha-blockers ($p < .01$). Differences in initiation were not statistically significant.

Anticholinergics were the only class of drugs for which there was a statistically significant difference in initiation: 8.33% of simple prostatectomy patients started taking them after surgery, compared to 7.89% of photovaporization patients, 5.74% of transurethral resection patients, and 4.76% of microwave or needle ablation patients ($p = .041$). The differences in discontinuation were not statistically significant for this class of drugs.

The differences in initiation and discontinuation were not significant for beta-3 agonists.

After 12 months, similar patterns persisted, with statistical significance increasing and some patients beginning to initiate new medications.

The class of drugs initiated the most was alpha-blockers; 51.6% of patients undergoing microwave or needle ablation started on these drugs. No patients started taking these drugs after undergoing simple prostatectomy. But 22.1% of photovaporization patients and 12.8% of transurethral resection patients initiated treatment with these drugs.

Overall, the microwave and needle ablation patients were the most likely to initiate medication after surgery, followed by the photovaporization patients, then the transurethral resection patients. The simple prostatectomy patients were the least likely to start drugs after surgery.

Each of the tissue-eliminating procedures has some advantages, said Dr. Gill.

“We’re in a good spot. We have a lot of different options,” he said UT.
‘Lift’ efficacious for enlarged median lobe

PUL procedure linked with improvements in symptoms, ejaculatory function

Cheryl Guttman Krader
UT Contributing Editor

SAN FRANCISCO—Results of the prospective MedLift study establish the efficacy and safety of the Prostatic Urethral Lift (PUL [UroLift System]) procedure for treatment of symptomatic BPH in men with an enlarged median lobe.

The 1-year clinical trial enrolled 45 men at nine centers. Presenting the findings at the AUA annual meeting in San Francisco, Daniel B. Rukstalis, MD, reported that PUL was associated with high patient satisfaction. Recovery occurred quickly after the procedure, and it led to statistically significant improvements in symptoms and ejaculatory function. Erectile function was preserved.

No patients required medications for BPH after the procedure, and there were no cases of serious device/procedure-related adverse events or de novo sustained erectile or ejaculatory dysfunction. “After the PUL was initially approved by the FDA, approximately 75% of men with prostates smaller than 80 cc would be considered candidates for this minimally invasive procedure. Based on the results of the MedLift study, we can now say that the PUL is applicable for men with all configurations of the prostate,” said Dr. Rukstalis, professor of urology at Wake Forest Baptist Medical Center, Winston-Salem, NC.

MedLift was conducted as a non-blinded, single-arm FDA Investigational Device Exemption extension of LIFT, the randomized clinical trial that led to FDA approval of the PUL procedure for men with enlarged lateral lobes of the prostate. Except for requiring that men have an obstructive median lobe, the MedLift inclusion criteria were identical to those in LIFT. To be eligible, patients had to be ≥50 years of age, have an International Prostate Symptom Score (IPSS) ≥13, peak flow rate (Qmax) ≤12 mL/s, prostate volume 30 cc to 80 cc, and prostate length 30 mm to 80 mm.

“At baseline, the participants in MedLift were similar to the LIFT patients except the MedLift patients were significantly younger and had significantly more voiding symptoms,” Dr. Rukstalis reported.

Men underwent flexible cystoscopy at baseline and 6 months and completed validated symptom and quality of life questionnaires at follow-up visits through 12 months. The extent of intravesical prostatic protrusion at baseline was categorized as <5 mm, 5-10 mm, and >10 mm using the baseline ultrasound image.

The outcomes evaluations showed that compared with baseline, the AUA Symptom Index score improved 58% at 6 months and 55% at 1 year; quality of life improved 60% at 6 months and 61% at 1 year; BPH Impact Index improved 75% at 6 months and 70% at 1 year; and Qmax improved 90% at 6 months and 108% at 1 year. Ejaculatory function evaluated with the Male Sexual Health Questionnaire improved 27% at 6 months and 39% at 1 year.

Lobe protrusion inconsequential

There was no statistically significant difference in symptom improvement based on the amount of middle lobe protrusion.

“This was surprising because the literature suggests that the degree of obstruction is related to the extent of middle lobe protrusion. The results would indicate that the PUL procedure can address a variety of presentations of the middle lobe,” Dr. Rukstalis said.

Comparing the results from MedLift and LIFT, Dr. Rukstalis noted that the MedLift patients had greater improvement in symptoms, quality of life, and peak flow.

“Published data from LIFT show that improvement in voiding symptoms was sustained for 3 years. MedLift follow-up is complete at 12 months, but we certainly anticipate that patients with an enlarged median lobe will follow this same pattern,” he said.

Most adverse events experienced by men in MedLift were mild to moderate in severity and resolved within 2 weeks. The most common adverse events were hematuria, dysuria, urgency, and urge incontinence. “The catheterization rate in MedLift was 80%, which is higher than in LIFT, but the median duration of catheterization was only 1.6 days,” Dr. Rukstalis said.

Data collected at 3 months showed 93% of patients would recommend the procedure.

NeoTract, Inc. provided funding for the study. Dr. Rukstalis is a meeting participant/lecturer for NeoTract. One of Dr. Rukstalis’ co-authors has several disclosures related to pharmaceutical/device companies, including serving as a consultant/adviser for PROCEPT BioRobotics and a consultant/adviser and meeting participant/lecturer for Teleflex.

Waterjet fares better vs. TURP in large prostates

Aquablation treatment delivers greater symptom score improvement, data indicate

Laird Harrison
UT CORRESPONDENT

SAN FRANCISCO—Men with large prostates experience more relief from BPH with treatment by Aquablation therapy (using the AquaBeam system) than with transurethral resection of the prostate (TURP), researchers say.

“Safety favors Aquablation,” Claus G. Roehrborn, MD, professor and chair of urology at the University of Texas Southwestern Medical School in Dallas, told Urology Times. He presented the findings at the AUA annual meeting in San Francisco.

Aquablation, which resects the prostate via robotic, high-velocity waterjet, can remove prostate tissue without applying heat. The procedure includes intraoperative transurethral ultrasound imaging and cystoscopic visualization. The surgeon creates a treatment plan prior to the therapy, then a robot executes the tissue removal while the patient is under general anesthesia.

A phase III randomized, clinical trial established that Aquablation can treat BPH more effectively than TURP, but researchers wanted to know whether it would work as well in men with particularly large prostates, defined as ≥50 mL to 80 mL. They analyzed subgroups pre-identified based on prostate volume.

Please see WATERJET, on page 6
Water vapor thermal Tx modestly improves BPH symptoms

Improvements are independent of presence of median lobe in real-life review

Laird Harrison
UT Correspondent

SAN FRANCISCO—Convective radiofrequency water vapor thermal therapy (Rezum) can modestly improve symptoms of BPH, according to Daniel Mollengarden, MD.

The new technology offers a minimally invasive alternative treatment that usually satisfies patients, said Dr. Mollengarden, MD, a fourth-year resident at University of Texas Southwestern Medical Center, working with Claus G. Roehrborn, MD, and colleagues.

Dr. Mollengarden presented a “real-life” retrospective review of a case series of 129 patients treated with convective radiofrequency water vapor using the Rezum device at the AUA annual meeting in San Francisco.

The procedure takes only 2 to 5 minutes to perform, said Dr. Mollengarden.

“This is a fairly novel technology. The big advantages are that it can be easily performed in the office, it can be used on any shape of prostate, and it preserves ejaculatory function,” he told Urology Times.

All the patients were treated by the same surgeon using local anesthesia. Twenty-five were part of the Rezum II trial. Median lobes were treated if present. The patients had a mean age of 67.4 years, prostate volume of 52.6 cc (ranging up to 86 cc), PSA of 2.45 ng/mL, maximum flow rate (Qmax) of 10.5 mL/sec, and post-void residual test of 106 mL.

Mean International Prostate Symptom Score (IPSS) was 18.3. Thirteen patients (10.4%) had an IPSS less than 8, 56 (44.8%) had an IPSS between 8 and 19, and 56 had an IPSS greater than 19. Ninety-seven patients (75.2%) were taking medication for BPH.

Mean IPSS dropped to 11.2 at 15-45 days after the procedure, then 8.5 from 46-90 days, and 6.9 at 90-180 days. Qmax increased to 13.2 mL/sec, then 16.3 mL/sec, and then 16.8 mL/sec over these time periods.

Ninety percent of the patients were no longer using BPH medication at the last follow-up. The average prostate shrunk by 17.9% using transrectal ultrasonography and 14.0% by PSA.

The improvements were independent of starting IPSS, treatment of a median lobe, and prostate size.

Majority of patients satisfied

Dr. Mollengarden and his colleagues administered a scripted patient questionnaire over the phone to gauge the patients’ satisfaction. Fifty-nine percent of the patients said they were very satisfied with the procedure, 18% satisfied, 10% neutral, 7% dissatisfied, and 6% very dissatisfied.

Forty-eight percent were very satisfied with the results, 25% were satisfied, 13% neutral, 4% dissatisfied, and 10% very dissatisfied. Eighty-six percent of patients would recommend the procedure to a friend.

The most common adverse event was a urinary tract infection, with 17.1% affected. A UTI was defined as 50,000 colony-forming units with symptoms. That was followed by urinary retention, which affected 14.0, and was transient in all cases. Cystoscopic evaluation of lower urinary tract symptoms was required in 7.8%. Events requiring anesthesia occurred in six patients.

“The authors are now starting to study glands larger than 80 grams.

“Currently, larger glands require more aggressive therapy. If we had a transurethral therapy that was effective for a large gland, that would be a nice part of the repertoire,” Dr. Mollengarden said.

Dr. Roehrborn was a paid investigator in a Rezum randomized clinical trial. Dr. Roehrborn is an investigator and meeting participant/lecturer for PROCEPT BioRobotics; a consultant/adviser, investigator, and meeting participant/lecturer for NeoTract, Inc.; and an investigator and consultant/adviser for NxThera, Inc. He has several other disclosures related to pharmaceutical companies.

WATERJET continued from page 5

Eighty-two men had prostates less than 50 mL and 102 had prostates at least 50 mL.

Among the men with large prostates, the mean baseline International Prostate Symptom Score (IPSS) was 22.2 for those randomly assigned to TURP and 22.9 for those randomly assigned to Aquablation (p=.43). The two groups were similar in age, body mass index, lobes, degree of middle lobe obstruction, and mean prostate volume: 52 mL for TURP versus 54 mL for Aquablation (p=.31).

Mean operative time was equivalent between the two groups: 32.8 minutes for Aquablation and 35 minutes for TURP (p=.28). But mean resection time was 4 minutes in the Aquablation group versus 28 minutes in the TURP group, a significant difference (p<.0001).

A Clavien-Dindo grade 1 persistent or grade 2 or higher event occurred in the first 3 months in 20% of Aquablation subjects and 46% of TURP subjects (p<.02).

At 180 days, men with a prostate volume >50 mL experienced an improvement in their IPSS scores of 17.4 points with Aquablation, compared to 13.3 points with TURP, which was statistically significant (p=.02).

Among the other findings:

• Men with a baseline flow rate of <9 mL/sec treated with Aquablation saw their IPSS score improve to 17.9 points, compared to 14.3 points with TURP, which was statistically significant (p=.03).

• Men with a middle lobe present treated with Aquablation attained an IPSS score of 19.9 compared to 11.0 with TURP, which was statistically significant (p=.005).

• Men with both larger prostates and lower flow rates (<9 mL/sec), experienced 7 points greater change in IPSS scores compared to TURP (p<.0001).

• For men with smaller prostates and greater maximum flow rates, the improvement in IPSS with TURP was 4.3 points larger than with Aquablation. However, this difference was not statistically significant (p=.0963).

PROCEPT BioRobotics provided funding for the study. Dr. Roehrborn is an investigator and meeting participant/lecturer for PROCEPT BioRobotics; a consultant/adviser, investigator, and meeting participant/lecturer for NeoTract, Inc.; and an investigator and consultant/adviser for NxThera, Inc. He has several other disclosures related to pharmaceutical companies. UT

Clinical Updates

FIGURE Water vapor therapy: Patient satisfaction with procedure

Source: Daniel Mollengarden, MD.
Statins beneficial in Caucasian men

Cheryl Guttman Krader
UT Contributing Editor

SAN FRANCISCO—A study investigating associations between statin use and prostate cancer outcomes provides further evidence that the medication may have race-related benefit, providing protective effects among Caucasian men but not in African-Americans of biochemical recurrence and that its protective prostatectomy was associated with reduced risk in African-Americans, investigators reported at the AUA annual meeting in San Francisco.

The research was conducted as a follow-up to a previous study that found statin use after radical prostatectomy was associated with significantly reduced risks for metastasis, CRPC, and PCSM among Caucasian men. No significant associations were found in African-Americans.

The findings of the race-stratified analysis were similar after adjusting for pathologic characteristics, although the associations in the Caucasian subgroup were no longer statistically significant, first author Emma H. Allott, PhD, told Urology Times.

Research will examine possible mechanisms

“For now, the results of our study are hypothesis-generating and suggest further research is warranted to investigate effects of statins in men with prostate cancer, as well as potential racial differences in these effects,” said Dr. Allott, lecturer in cancer epidemiology at Queen’s University Belfast, Northern Ireland.

“We are in the process of updating our database so that our study may have more power, and then we will see if the suggested associations between statin use and outcomes in white men remain significant in the multivariable adjusted analysis. Going forward, we are also trying to understand the mechanisms that might underlie racial differences,” added Dr. Allott.

In a multivariable analysis adjusting for demographic, clinical, and pathologic characteristics, no associations were found between pre-ADT statin use and any of the outcomes when considering the overall population. In a race-stratified univariable analysis, statin use prior to ADT was associated with significantly reduced risks for metastasis, CRPC, and PCSM among Caucasian men. No significant associations were found in African-Americans.

Dr. Padmanabhan joins UT editorial council

Urology Times is pleased to announce the appointment of Priya Padmanabhan, MD, MPH, to its Editorial Council, where she will serve as our expert in female urology. Dr. Padmanabhan is associate professor of urology at the University of Kansas School of Medicine, Kansas City. She is also a staff surgeon at the Kansas Veterans Administration Hospital and two other local hospitals. Her clinical and research interests include genitourinary reconstruction, lower urinary tract dysfunction, neurogenic bladder, and robotic surgery, with a focus on quality of life issues.

The Urology Times editorial staff also extends its thanks and appreciation to Shlomo Raz, MD, for 20-plus years of dedicated service to the publication’s Editorial Council. Dr. Raz retired from the UCLA School of Medicine department of urology in June 2018.
Positive data reported for urothelial Ca agent

John Schieszer
UT Correspondent

SAN FRANCISCO—Clinicians may soon have a new non-surgical approach to offer patients with low-grade upper tract urothelial cancer (UTUC).

Researchers presented findings at the AUA annual meeting in San Francisco demonstrating that UGN-101 (MitoGel), an investigational mitomycin formulation, may be a new non-surgical treatment option for patients with UTUC. The interim analysis from the ongoing international multicenter phase III OLYMPUS clinical trial showed a complete response rate of 59% in 34 patients who were evaluated for primary disease evaluation (PDE), which was the primary endpoint. PDE involves the use of ureteroscopy and wash cytology.

PDE was conducted 4 to 6 weeks after completion of UGN-101 treatment, which was administered once weekly for 6 weeks. The authors found that 20 of the interim analysis intent-to-treat population achieved a complete response, which was defined as a negative ureteroscopic evaluation and a negative wash cytology. In addition, five of 34 patients (15%) achieved a partial response.

“The complete responses have been durable at 3-month follow-up, 6 months, and 9 months. The high initial complete response rate and durability observed in the interim analysis is very promising and suggests that UGN-101 could be an effective and well-tolerated noninvasive treatment for patients with UTUC, potentially sparing them from invasive surgery to remove their kidney,” said principal study investigator Seth Paul Lerner, MD, professor of urology at Baylor College of Medicine, Houston.

In this current investigation, approximately 39% of tumors treated were categorized as unresectable by surgery at baseline. Among the 20 patients who achieved a complete response, 13 patients have reached 3-month follow-up and all remain in complete response. Four of these 13 patients have reached 6-month follow-up and one has reached 9-month follow-up. All remain in complete response.

Treatment well tolerated

UGN-101 appeared to be well tolerated, with most treatment-emergent adverse events characterized as mild or moderate and transient. Adverse events included urinary tract infection, flank pain, ureteral narrowing and hydronephrosis, and time-limited creatinine elevation. Mark Schoenberg, MD, chief medical officer of UroGen, said these findings are promising and demonstrate the potential of UGN-101 to become the first drug ever approved for low-grade UTUC.

“It could be approved in the next 6 to 9 months,” Dr. Schoenberg said in an interview with Urology Times.

OLYMPUS (Optimized DeLivery of Mitomycin for Primary UTUC Study) is an open-label, single-arm phase III clinical trial of UGN-101 and is anticipated to enroll approximately 74 patients at clinical sites across the United States and Israel. UGN-101 is an investigational drug formulation of mitomycin that utilizes the RTGel technology platform, UroGen’s proprietary sustained-release, hydrogel-based formulation. This is designed to allow longer exposure of mitomycin to the urinary tract tissue, thereby potentially enabling the treatment of tumors via non-surgical means. The FDA has granted both Orphan Drug and Fast Track designations to UGN-101 for the treatment of low-grade UTUC.

“The high initial complete response rate and durability observed in the interim analysis is very promising and suggests that UGN-101 could be an effective and well-tolerated noninvasive treatment for patients with UTUC.”

SETH PAUL LERNER, MD

“Despite advances in endoscopic management of low-grade UTUC, nephrectomy is often required to manage recurrent, large-volume, or inaccessible tumors in the renal pelvis. The high complete response rate observed in this interim analysis is encouraging and, if borne out through the rest of the trial and consistently durable, these data suggest that this novel chemoablation treatment approach may help patients avoid or delay the need for nephrectomy,” Dr. Lerner told Urology Times.

Dr. Lerner has received compensation for serving on a UroGen advisory board, and his institution receives funds for his role as principal investigator of the OLYMPUS trial.

STATINS

continued from page 7

ences in the effects of statins in men with prostate cancer,” added Dr. Allott, previously assistant professor of nutrition, University of North Carolina, Chapel Hill and John Fitzpatrick Research Fellow, Trinity College Dublin.

The research was conducted using the Veterans Affairs hospitals’ Shared Equal Access Regional Cancer Hospital (SEARCH) database, headed by Stephen Freedland, MD, of Cedars-Sinai Medical Center, Los Angeles. The analysis of the impact of pre-ADT statin use on prostate cancer outcomes included 570 men, of whom 42% were African-American and 54% were pre-ADT statin users.

Compared with the non-statin users, statin users were older, had a higher body mass index, and had a shorter median follow-up. There were no significant differences between the statin users and non-users in racial distribution, pathologic findings at radical prostatectomy, or pre-ADT PSA levels.

The idea that statin use can have a positive effect on prostate cancer outcomes considers their activity for inhibiting production of cholesterol.

“Cholesterol is the precursor for synthesis of sex hormones that may sustain androgen-dependent tumor growth, even in men who achieve castrate serum levels while on ADT,” Dr. Allott said.

She proposed that race-related genetic and genomic differences in tumor biology might account for potential race-related differences in effects of statin use on prostate cancer outcomes.

“There has been little research investigating which molecular subtypes of prostate cancer might be more sensitive to statins. Going forward, we are incorporating molecular tumor profiling in our studies as we try to tease apart the mechanisms,” she said.

Alternatively, the differences observed in Caucasian and African-American men may be non-biologic and related to unmeasured or unadjusted variables.

“For example, there could be differences in comorbidities between the racial groups that are influencing outcomes. By updating our database, we hope that we can adjust for more potential confounders,” Dr. Allott said.
**Weck® Hem-o-lok® Polymer Ligation System**

We’ll put our numbers up against anyone.

---

**Why do surgeons trust Weck Hem-o-lok Clips for security?**

- **The #1 selling locking polymer clip**, used in millions of patients worldwide.
- **Over 70 articles** in peer-reviewed journals showed favorable outcomes in support of Hem-o-lok Clips*.
- **Available in 4 sizes**, fitting tissue structures 2-16 mm.
- **Since 2007**, we’ve collaborated with Intuitive Surgical to provide the Hem-o-lok System for use with the *da Vinci®* Surgical System.
- **Based on an ex vivo study,** Hem-o-lok Clips provide **unparalleled security** compared to leading competitors in three common clip failure modes.

---

**Learn more at Teleflex.link/HOL-UroTimes**

---

*Based on a tertiary clinical literature search performed 11/2014. 89 peer-reviewed articles were accepted according to Inclusion/Exclusion criteria, of which 80% (71 articles) showed favorable outcomes in support of Hem-o-lok Clips. Data on file, Teleflex Incorporated, Report #MLIB-000588.

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

Hem-o-lok Clips are not intended for use as a fallopian contraceptive tubal occlusion device.

Hem-o-lok Clips are contraindicated for use in ligating the renal artery during laparoscopic donor nephrectomy.

*da Vinci* is a registered trademark of Intuitive Surgical.

Teleflex, the Teleflex logo, Endo®, Hem-o-lok, and Weck are registered trademarks of Teleflex Incorporated or its affiliates.

© 2018 Teleflex Incorporated. All rights reserved. MC-000833 Rev 1
5-ARI use reduces prostate Ca risk for up to 16 years

No decrease in beneficial effect over time, recent study findings indicate

The Prostate Cancer Prevention Trial (PCPT) was a placebo-controlled, double-blind randomized controlled trial showing that using the 5-alpha-reductase inhibitor finasteride (Proscar), 5 mg daily for 7 years, could reduce the risk of prostate cancer by 25%. The trial duration was limited to 7 years of treatment and follow-up due to the substantial cost and burden of randomized controlled trials. However, some questions had emerged, such as whether the trial duration was sufficient to demonstrate the maximum benefit of finasteride. Another concern was whether the reduced risk of prostate cancer would be maintained after discontinuation of finasteride at the end of the trial.

A recent report by Unger et al, using the innovative approach of linking the PCPT clinical data with Medicare claims, confirms that the beneficial effect of finasteride in reducing the risk of prostate cancer is maintained for up to 16 years (J Natl Cancer Inst 2018; 110:djy035).

In order to determine the risk of prostate cancer beyond the 7-year study period, the authors linked the PCPT clinical records to the participants’ Medicare claims data using Social Security number and date of birth. This linkage allowed the diagnosed prostate cancer to be identified by both the clinical records and the Medicare claims.

Of the 18,880 PCPT participants (finasteride: 9,423; placebo: 9,457), 14,176 (75.1%) had a linkage to Medicare claims (finasteride: 7,069; placebo: 7,107). The time interval from randomization in the PCPT to the end of Medicare coverage for the men linked to the Medicare database was a median 16 years for both groups. The authors analyzed the prostate cancer risk over three follow-up periods: 0-6.5 years, 6.5-7.5 years (to account for the end-of-study biopsy-detected prostate cancer), and after 7.5 years (to assess the prostate cancer risk after the completion of the trial).

While there was no further reduction of prostate cancer risk after finasteride was discontinued, there was also no evidence that stopping finasteride resulted in more cases of prostate cancer.

Over the entire follow-up period, the cumulative incidence of prostate cancer was 22.3% in the placebo arm and 18.1% in the finasteride arm. In the first 7.5 years, the finasteride arm had a 29.1% lower hazard ratio for prostate cancer diagnosis. However, after 7.5 years, the risk was stable and there was no statistical increase or decrease in the prostate cancer risk.

21.1% decrease in HR observed

During the entire follow-up, finasteride arm participants had a 21.1% decrease in the hazard ratio of prostate cancer. The hazard ratio for prostate cancer development remained in favor of finasteride during all the follow-up windows (0-6.5; 6.5-7.5; 7.5-16 years); ie, there was no decrease in the beneficial effect of finasteride over time, even after the trial had ended.

This interesting and novel use of secondary data sources can enhance our ability to detect long-term outcomes of clinical trials. The PCPT is especially suited for this linkage approach because the age for PCPT participation was 55 years and Medicare enrollees are 65 years of age or older. The use of Medicare claims data linked to clinical trials data to provide long-term follow-up of trial participants can help answer some of the questions mentioned above in a relatively low-risk manner, with minimal cost.

Finasteride use lowered the risk of prostate cancer both prior to and including the 7-year biopsy period (25.2% and 29.1%, respectively). While there was no further reduction of prostate cancer risk after finasteride was discontinued, there was also no evidence that stopping finasteride resulted in more cases of prostate cancer. This would confirm that finasteride prevented the development of prostate cancer and not simply delayed the diagnosis of prostate cancer.

A significant gap in knowledge and a limitation of this report is the lack of Gleason grade to distinguish high-grade cancers over time. While the initial results reported a higher incidence of high-grade prostate cancer in the finasteride group, this concern should have been alleviated by a number of subsequent reports showing no change in adverse outcomes or mortality. Further, Medicare claims for the use of oral medications such as finasteride were not available previously, so it’s possible that some men may have restarted finasteride.

It appears that the prostate cancer risk reduction by finasteride use for a limited number of years may continue over the long term (21.1% decreased risk for a median of 16 years). Hopefully, this and previous research confirming the long-term reduction in prostate cancer diagnosis will give urologists a strong reason to take a second look at the use of finasteride for prostate cancer prevention.
Opportunistic salpingectomy in female urologic surgery
Evidence suggests fallopian tube removal will lead to reduced ovarian cancer incidence

Opportunistic salpingectomy (OS), the removal of fallopian tubes at the time of hysterectomy for non-cancer indications, has emerged over the past 2 decades as a promising procedure for reducing the risk of ovarian cancer. While definitive evidence of the benefit of OS in ovarian cancer prevention remains to be had, the current supporting literature is compelling and this practice is being evaluated for other types of surgery. (Also see, “Ovarian cancer risk and OS: Current evidence,” page 12.)

In 2018, a survey of female pelvic medicine and reconstructive surgeons found that 82% of respondents discuss and/or perform OS at the time of pelvic organ prolapse repair (Int Urogynecol J April 14, 2018 [Epub ahead of print]). However, the sample size was small and did not include urologic surgeons. Given that over 200,000 prolapse procedures are performed annually, many of which are performed by urologists, there is an opportunity for including salpingectomy at the time of these procedures.

This article discusses surgical approaches to OS for urologists, risks of surgery, and cost.

Procedure steps
The current recommendation for OS is that the entire tube be removed. However, in cases when this is not feasible, such as adhesive disease or vaginal repair, removing the distal one-third of the fallopian tube, which includes the fimbria, is thought to be sufficient.

Laparoscopic approach. Salpingectomy may be performed before or after pelvic reconstruction. The laparoscopic approach is as follows:

The fimbriated end of the fallopian tube (figure 1) is grasped with an atraumatic grasper such as an Allys clamp. The fallopian tube is then separated from the mesosalpinx (figure 1) using a vessel-sealing device such as a LigaSure. Care should be taken to perform the mesosalpingeal dissection close to the fallopian tube to avoid injuring the infundibulopelvic ligament, which contains the ovarian artery and disrupting ovarian anastomotic vessels within the broad ligament (figure 1, yellow arrow). The vessel-sealing device is then used to dissect the fallopian tube off the mesosalpinx, moving proximally toward the cornua. Salpingectomy is started by dissecting the fimbria off the mesosalpinx as closely as possible without compromising the infundibulopelvic ligament.

Figure 1 / Laparoscopic view of right adnexa demonstrating the ovary (red arrow), infundibulopelvic ligament (yellow arrow) and fimbriated end of the fallopian tube (blue arrow). Salpingectomy is started by dissecting the fimbria off the mesosalpinx as closely as possible without compromising the infundibulopelvic ligament.

Figure 2 / Dissection of the fallopian tube (red arrow) from the mesosalpinx (blue arrow) is performed moving proximally toward the cornua. The infundibulopelvic ligament (yellow arrow) is now well away from the area of dissection and cautery affect. (Photos courtesy of David Sheyn, MD, and Adonis Hijaz, MD)
SALPINGECTOMY

continued from page 11

the uterine cornua (figure 2). It is then transected, after cautzeriation, approximately 1 cm to 2 cm from the cornua (figure 3). The tubal segment can be removed through a 5-mm or larger diameter port in most circumstances. The same procedure may be performed starting at the cornual end of the fallopian tube, 1 cm to 2 cm from the cornua itself, and dissecting the tube off of the mesosalpinx distally toward the fimbria.

Laparotomy. The procedure may also be performed via laparotomy in a similar fashion, but dissection of the tube from the mesosalpinx can be accomplished using monopolar cautery and the tube is ligated with a 0 or 2-0 vicryl suture near the cornua. Both the abdominal and laparoscopic approaches may be performed in a similar fashion during non-gynecologic surgeries.

Vaginal approach. The vaginal approach for salpingectomy may be more challenging and can usually be performed after vaginal hysterectomy. A right-angle retractor is used to retract the ipsilateral side-wall, and a sponge stick is used to retract the bowel away from the fallopian tube. The fimbria is grasped with a Babcock clamp and cross clamped with either a Haney or Kelly clamp. It is not usually feasible to remove the full length of the tube via the vaginal approach, and studies have shown removal of the distal third of the fallopian tube is sufficient for OS.

The gynecologic and urogynecologic literature has shown that vaginal salpingectomy does not appreciably increase operative times or bleed-

OVARIAN CANCER RISK AND OS: CURRENT EVIDENCE

There are 20,000 new cases of epithelial ovarian cancer diagnosed annually in the United States. While ovarian cancer accounts for fewer than 3% of cancers in women, it is the fifth most common cause of death in women from any cancer and the most common cause of death from gynecologic cancer. Survival, which is between 19% and 48% at 5 years depending on stage at diagnosis, has not changed appreciably in the past 3 decades.

One major reason for this is that ovarian cancer is most often diagnosed in advanced stages because it is often asymptomatic in early stages and effective screening strategies are lacking. Epithelial ovarian cancer has multiple subtypes, with the serous subtype being the most common (70% of all cases). Over the past 2 decades, histologic evidence has suggested that serous epithelial ovarian cancer arises from precursor lesions within the fallopian tubes, termed serous tubal intraepithelial carcinomas (STIC), rather than from the ovary itself. The exact percentage of epithelial ovarian cancers arising from STIC lesions is not entirely clear but is currently estimated at 50%.

Over this same time period, multiple population-based studies demonstrated that female sterilization procedures—which include removal of a mid-tubal segment and occlusion with various devices including silicone rings and titanium clips or total removal of the fallopian tube—are associated with significant reductions in epithelial ovarian cancer incidence. Based on these findings, in 2010 the British Columbia Ovarian Cancer Research team developed and distributed an educational video to promote the practice of removing fallopian tubes at the time of hysterectomy for non-cancer indications, a practice termed opportunistic salpingectomy (OS). Since that time, this practice has gained widespread acceptance among gynecologic surgeons who perform hysterectomies and, in some cases, sterilization procedures.

OS refers to the removal of fallopian tubes in women who have a general population lifetime risk of developing ovarian cancer, which is around 1.5%. The American College of Obstetricians and Gynecologists (ACOG) currently does not make specific recommendations regarding OS, stating only that the risks and benefits should be discussed with patients and that surgical planning should not change based on whether or not a salpingectomy will be performed. However, a 2017 ACOG survey showed that 75% of gynecologists perform OS at the time of hysterectomy.

—David Sheyn, MD, and Adonis Hijaz, MD

Figure 3 / The fallopian tube (yellow arrow) is amputated 1 to 2 cm from its insertion into the uterine cornua (red arrow). (Photo courtesy of David Sheyn, MD, and Adonis Hijaz, MD)

Figure 4 / Blood supply of the uterus and adnexa (Illustration courtesy of Robert Pollard, MD, MetroHealth Medical Center, Cleveland)
Risks of opportunistic salpingectomy

While OS has been rapidly adopted by the gynecologic community over a relatively short time period due to the promise of preventing a cancer that is difficult to diagnose and treat, at this time there is no evidence that OS has led or will lead to a reduction in the incidence of ovarian cancer, and this data is likely still at least a decade away. Furthermore, some surgeons have concerns about long-term consequences of salpingectomy with ovarian conservation.

Figure 4 shows the blood supply of the uterus, ovaries, and fallopian tubes. It is clear from the schematic that there is significant potential for the disruption of ovarian blood supply with salpingectomy. There has been concern that salpingectomy in premenopausal women could lead to earlier onset of menopause and resulting consequences of vasomotor symptoms, increased cardiovascular disease risk, and osteoporosis. However, studies evaluating anti-Müllerian hormone levels (a proxy of ovarian function), postoperative ovarian blood flow, and onset of menopausal symptoms have not shown a difference in women who did and did not have salpingectomy. Increasing health care costs have also been cited as a possible result of salpingectomy, particularly in the absence of tangible risk reduction. Presently, studies have shown that at the time of hysterectomy, salpingectomy does not increase the cost of the procedure, but salpingectomy for sterilization has been shown to be less cost-effective than tubal ligation. Studies evaluating cost of salpingectomy at the time of pelvic floor reconstruction and non-gynecologic procedures are lacking.

Conclusion

Opportunistic salpingectomy has rapidly emerged as a promising procedure for the reduction of ovarian cancer. While definitive evidence of risk reduction is currently lacking, large-scale studies of tubal sterilization patients and salpingectomy for non-risk-reducing indications have strongly indicated the removal of the fallopian tube will lead to a reduction in the incidence of ovarian cancer.

While more study must be done before there is universal adoption of this procedure, there is evidence to suggest that incorporation of salpingectomy into female pelvic reconstructive surgery is safe and will not lead to an appreciable increase in health care costs.

VAGINAL MESH SURGERY: CAREFUL PATIENT SELECTION KEY

The high number of reported complications from transvaginal repairs for pelvic organ prolapse using vaginal mesh have led to a significant decline in its use, despite its initial promise. Following a 6-year analysis of California records of pelvic organ prolapse repairs, investigators reporting in the Journal of Urology conclude that use of vaginal mesh may be appropriate in specific cases provided the risk of surgical complications is carefully weighed against the risk of repeat surgery for recurrent prolapse (J Urol 2018; 200:389-96).

“Early research on vaginal mesh demonstrated excellent results similar to our trusted midurethral slings, so we rejoiced at the opportunity to offer women a longer term reliable prolapse repair option and incorporated these procedures into our practice,” explained lead investigator Christopher S. Elliott, MD, PhD, of Stanford School of Medicine, Stanford, CA, and Santa Clara Valley Medical Center, San Jose, CA.

However, while the story of vaginal mesh was still in its infancy, reports of complications unique to vaginal mesh prolapse procedures suggested greater than expected problems. Specifically, it was suggested that complications might be associated with synthetic mesh itself, surgical technique, or patient-specific characteristics. This study focuses on these three specific causes on a population-specific level.

Investigators used data from the U.S. Office of State Health Planning and Development to review the records of more than 110,000 women in California who underwent a pelvic organ prolapse repair from 2005-2011 (with and without a synthetic mesh). Sixteen percent underwent mesh augmentation. They chose this study period to reduce any bias that a 2011 FDA warning on mesh use might have created. They then identified all women who underwent a repeat surgery for either recurrent pelvic organ prolapse or a mesh complication.

The authors found that neither mesh use itself nor surgeon experience was independently associated with the risk of a repeat surgery. Rather, it was likely related to placing mesh in a specific subset of women. Their data indicated that vaginal mesh use for pelvic organ prolapse repair may be appropriate on a population level, specifically if strategies to balance the risk of surgical complication versus the risk of surgery for recurrent prolapse are used.

“Our results show that the mesh itself and surgeon experience do not appear to be the problem, rather we may not be choosing wisely who receives a mesh implant,” concluded Dr. Elliott. “We hope our results can be used as a benchmark of first-generation mesh outcomes to compare to future generations of vaginal prolapse mesh and further the discussion of vaginal mesh use for prolapse in light of recent negative reports.”

“The saying ‘Hindsight is 20/20’ is an appropriate one in the setting of POP surgery,” commented Alexander Gomelsky, MD, of Louisiana State University Health-Shreveport. “It is quite reassuring that in the right hands, mesh surgery for POP can lead to a positive benefit-to-risk ratio. However, the right patient for these operations currently remains largely in our hindsight.”

Pelvic organ prolapse affects 30%-50% of women in their lifetime, with around 2% developing symptoms. Transvaginal repairs using vaginal mesh were first used in the United States in the 1990s and were approved by the FDA in 2002. In 2010, at least 100,000 transvaginal mesh procedures were performed in the U.S. However, the increasing number of complications reported to MAUDE (Manufacturer and User Facility Device Experience), including infection, bleeding, painful sexual intercourse, recurrence of pelvic organ prolapse and urinary incontinence, and three deaths attributed to mesh complications, led to a strongly worded warning from the FDA in late 2011 that concluded that the complications exceeded any benefits. Its use has since declined significantly internationally alongside an increase in litigation and the withdrawal of several products from the market.
Focal therapy for prostate Ca: Ready for prime time?

**Q:** Please define focal therapy for prostate cancer in its current format.

**A:** I think it’s important to look at two different, related concepts. The first, which I think is the most critical, is agreeing on what is focal and what is not. Three strategies have been tested in various forms. One is true lesion-directed therapy, which assumes the patient has a positive MRI and an ablation source will be directed at it, plus or minus a defined margin, and that’s probably going to be surgeon dependent. The other two—hemablation and “hockey-stick” ablation—are not necessarily historically image guided. There is published experience with both approaches in patients with a low-volume, unilateral biopsy.

Dr. John Ward of MD Anderson worked on the hockey-stick approach over 10 years ago. He found that by studying radical prostatectomy specimens, if you had a patient with unilateral cancer and wanted to address the dominant and most of the secondary tumors, it was necessary to treat the affected side completely and the anterior contralateral side. You might say that shouldn’t be called focal therapy because it’s subtotal therapy, and that’s a fair criticism. Although I haven’t seen data on it, I would imagine it would affect how much residual PSA you will be measuring when you’re treating 25% versus 75% of a gland.

The second concept where there is less controversy involves seven ablation sources: cryotherapy, high-intensity focused ultrasound (HIFU), laser ablation (which assumes real-time MR monitoring), photodynamic therapy, irreversible electroporation, brachytherapy, and radiofrequency ablation.

**Q:** What are the perceived advantages of focal therapy?

**A:** The one that is the least controversial is quality of life. Compared to standard, full-gland treatment with surgery or radiotherapy, patients will have less reduction in sexual function and possibly fewer irritative side effects. That probably applies to the range of focal and subtotal approaches I mentioned. There’s plenty of literature on cryotherapy with hockey stick showing that if you leave one entire posterolateral zone alone, patients will have fairly reasonable maintenance of sexual function.

**Q:** When you mention laser ablation, what type of laser are you talking about?

**A:** They are not identical to holmium or GreenLight type applications for benign disease. These are termed “laser interstitial theromotherapy” that are either continuous wave or pulsed. The mechanisms are the same—thermal coagulation, vascular damage, and finally, cellular damage.

**Q:** What are the limitations? One that comes to mind is that I’ve always been concerned about is men with a large gland, whom I’m hesitant to treat with radiation therapy or brachytherapy. Do we see the same limitation with focal therapy?

**A:** Regarding men with large glands, that may be a little more technique based. In cryotherapy and brachytherapy where templates are used, there will probably still be an upper limit of prostate size; ie, my comment regarding brachytherapy selection. In the laser and some of the other procedures that are perhaps more in-bore, MRI-based, you probably can be a little more creative about what you can access. The techniques are evolving and in some cases premature; ie, some patients may have an Artemis robot-driven biopsy, and yet their actual treatment is somewhat freehand the way it’s commonly applied.

**Q:** Are there other limitations? For instance, what about bleeding and incontinence?

**A:** Those events are going to be favorable and similar to what is seen with active surveillance. Keep in mind, though, that even an active surveillance cohort will show very subtle declines in sexual function over time, but that is very minimal and probably just related to aging.

One criticism may come from high-volume surgeons who live in a world of constantly seeing image results and pathology results in the circle of planning therapy. Specifically, MRI is an estimation of what’s going on in the prostate. It does not have the precision yet that people want it to have. One particular paper in the *Journal of Urology* (2017; 197:320-6) used a modeling system of what a full radical prostatectomy speci-
FOCAL THERAPY / Q&A

What would you tell practicing urologists about counseling their patients and referring them to an academic center?

J. BRANTLEY THRASHER, MD

If you have patients who really want to pursue focal therapy, I would determine who in your community is doing this on a registry or a trial and develop a partnership in that direction.

Q: Whom do you consider the ideal candidate for focal therapy today?

A: The same question applies to whether or not we should be using biomarkers in prostate cancer, such as Prolaris or Oncotype. If you apply those to low-volume, Gleason 6 tumors, there aren’t many events already so it’s difficult for the biomarker to affect long-term endpoints. The same dynamic exists with focal therapy. If you apply it to a Gleason 6 tumor, you’ll have a hard time finding an oncologic benefit. You may be able to simplify patients’ monitoring compared to active surveillance, but you’re not going to be able to affect prostate cancer mortality.

There’s some potential for selecting Gleason 7 patients, especially those with favorable-risk, intermediate disease. These are mostly patients with Gleason 3+4 disease that can be reasonably defined in imaging and can be treated with the idea of converting their disease to a low-volume Gleason 6 tumor. If you do truly lesion-directed therapy, some satellite non-significant tumors will probably be ignored. You will have detectable PSA to interpret and you’ll probably still have to do some biopsy- and image-related follow-up testing.

The weakness of active surveillance for some patients is that they feel like they’re just waiting around for something bad to happen as opposed to proactively changing it. For focal therapy, I think most experts in the field—and some Delphi consensus panels have been published on this (Prostate Cancer Prostatic Dis 2017; 20:294-9)—have defined the intermediate, especially favorable intermediate-risk patient, as the ideal patient. I don’t think the choice of focal therapy has to be age dependent, but older age and comorbidity might make more sense.

Q: Are we really treating these patients emotionally, or do we have good outcome data suggesting we’re making a difference with focal therapy in patients with Gleason 3+4 low-volume cancer?

A: The data will take time. I would lean on the surveillance outcome data from Dr. Laurence Klotz because, even in his series, the Gleason 3+4s typically have a slow pathway but when they hit that 10-year mark and beyond, there tends to be an uptick on conversion to therapy. The mortality statistics are still very low, but to the extent that frequency of biopsies could be reduced and quality of life maintained, that’s where you could probably carve out a benefit. Would biomarkers help in that space? Maybe. There is potential there as well.

Q: What do the AUA/ASTRO/SUO guidelines say on the topic?

A: The guidelines on localized prostate cancer were announced and discussed at the 2017 AUA annual meeting and were published this year in two parts in the Journal of Urology (2018; 199:683-90 and 2018; 199:990–9). The guidelines basically recommend that focal therapies are not standard and really should be done on a trial. It would be fair to say a trial can be somewhat loosely defined. One definition is a direct comparative trial, which would be the best, and the lack of comparative evidence was what the AUA panel was concerned about.

A trial could also include a registry. A recent Journal of Urology paper discusses the creation of a national online registry by a group of experts (J Urol 2018; 199:1488-93). At this time, there are no data in the publication, but it shows the defined and agreed-upon endpoints of focal therapy that practitioners should be recording. From that, clinicians can start crafting questions.

Q: Is knowing this information also a benefit because we have potential competing interests in this space, including interventional radiologists and possibly medical oncologists? Since urologists have been known as the experts and the champions of this space, is it important to refer within the specialty?

A: As someone who was part of the early wave of robotic surgery that clearly rolled out without high-level evidence, you could draw a parallel argument. Are we holding focal therapy to a higher standard than the other treatments? It’s a question that’s somewhat fair.

But part of the reason why we need to be strict about rolling out focal therapy is that the endpoints we’ve used in prostate cancer are very long term. If you do a robotic prostatectomy, you get a pathology report and perioperative outcomes, for example. If clinicians start applying focal therapy to aggressive disease, we don’t know what that means biologically; I’ve clearly seen people come back with metastatic relapse within 2 years. Perhaps that would have happened anyway, but if that is being done with no trial or comparative registry, there is potential for harm.

Q: What happens if focal therapy fails, and what PSA criteria are you using for recurrence?

A: Regarding PSA recurrence, I don’t think

Please see FOCAL THERAPY, page 16
Q&A / FOCAL THERAPY

FOCAL THERAPY

continued from page 15

there is agreement on it. I don’t think you can apply the Phoenix definition because that was developed out of full-gland radiation dosage. Most of it comes out of repeat biopsy and repeat imaging. In almost all the men I’ve treated for salvage, it’s been biopsy generated. The PSA may set the stage for how concerned we are, but all patients should probably undergo a 1-year biopsy, and these are the types of parameters the registries are working on.

The salvage HIFU and cryotherapy literature would suggest that, with experts doing the salvage therapy, urinary control is probably going to be OK. I do think sexual function will take a hit. With the less and less intensive, true lesion-directed focal therapies, we don’t know yet about adverse events with salvage therapy. Hypothetically their salvage surgery might be better. Then there’s the option, as in some of the older patients who have failed, to radiate. And some of these focal therapies can be repeated.

Q: When we talked about measurement for recurrence, you said biopsy will be critical. We have a difficult time obtaining a Gleason sum in patients after radiation. Can we still use a Gleason grading system when we re-biopsy after using the focal therapies you mention?

A: Yes and no. Obviously some of those recurrences are going to be out of field and valid for that reason. With some of the in-field recurrences, pathologists will hedge a little bit; they’ll give you a Gleason score but say there’s treatment effect there. We do have data from salvage radiation that, even if they can’t obtain a Gleason score on radiated patients, if they see residual tumor, it is usually real, not just dead cells.

Q: I hear there are 5 Tesla and 6 Tesla MRI scanners out there now. Will imaging change this in the future?

A: I think imaging will have to improve if we’re going to move to a lesion-directed philosophy. We’re going to have to see a little better. These tumors are not perfectly round circles like they appear on an MRI. The real growths tend to be very scattered, so the better you can draw out a template, the better. As surgeons, we always struggle with the fact that when we see pathology results, the dominant tumor is not always the aggressive one. It can be the second or third largest tumor foci.

Q: Do you have any take-home messages for practicing urologists about focal therapy? Where do you see it fitting into practice?

A: I think the AUA guidelines will help you to define standards versus alternatives, and I recommend being well versed in that. Have a plan for how you would refer patients or perhaps your group will have a designated expert. There will be how-to courses and trial workshops. The AUA currently is sticking to more of the educational plan. I think that’s what is sufficient for now. I think this is going to be a small but growing field.

NO SURVIVAL BENEFIT SEEN WITH PSA-TARGETED VACCINE IN mCRPC

Leah Lawrence / UT Contributor

Ms. Lawrence is a contributor to Urology Times sister brand Cancer Network, where this article was originally published.

No overall survival (OS) benefit was seen for patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (CRPC) treated with the PSA-targeted, poxvirus-based cancer vaccine PROSTVAC-V/F (PRO) compared with placebo, according to results of the PROSPECT trial.

PROSPECT was designed to be a confirmatory trial conducted following a phase II trial that showed an 8.5-month improvement in OS with PRO compared with placebo. However, after a third interim analysis, the data monitoring committee recommended closure of PROSPECT on the grounds of futility.

The results were presented by James L. Gulley, MD, of the National Cancer Institute, Rockville, MD, at the American Society of Clinical Oncology annual meeting in Chicago.

PROSPECT randomly assigned 1,297 patients with asymptomatic or minimally symptomatic metastatic CRPC to one of three arms: PRO plus placebo, PRO plus granulocyte-macrophage colony-stimulating factor (GM-CSF), or double placebo. The vaccine was given in week 1, and patients received six subsequent boost vaccinations over a period of 5 months. OS was the primary endpoint.

Patients received most treatments though week 13, with a slight decrease thereafter. At the time of the third interim analysis, the OS curves for the intent-to-treat population overlapped. The hazard ratio (HR) for PROSTVAC compared with placebo was 1.0058; for PROSTVAC plus GM-CSF compared with placebo, HR was 1.0202. Median OS was between 33.2 months and 34.4 months.

“...The overall survival observed in all arms was approximately 1 year longer than anticipated based on historical controls and the prior randomized phase II trial,” Dr. Gulley said. “This was likely due to improved standard of care as study enrollment began in 2011.”

In a subgroup analysis, the authors found no difference between the treatment arms for any of the groups analyzed. In addition, there was no difference between study arms for event-free survival, a secondary endpoint.

Toxicity was also similar between the groups of patients. Common adverse events included injection site reactions, fatigue, chills, influenza-like illness, and pyrexia. Pyrexia and injection site reaction were slightly more common among patients who received GM-CSF. Serious treatment-emergent adverse events were seen in less than 1% of patients.

Discussing the results of the trial, Douglas G. McNeel, MD, PhD, of the University of Wisconsin School of Medicine and Public Health, Madison asked, “What happened here?”

“There was a lot of excitement about this trial based on the phase II trial from 2010, which showed a very significant difference in overall survival between these groups,” Dr. McNeel said. “If you look at that trial compared with what you currently see, the control population was markedly different and had almost a doubling of overall survival. The fact is that things have changed since 2010.”

Daniel G. Chong, MD, of Virginia Cancer Specialists, Fairfax, commented, “This is yet another promising study demonstrating that using the immune system to treat advanced prostate cancer does not produce the same effectiveness as is seen in other cancer types, and we may need to use other techniques to make prostate cancer more immunogenic to checkpoint inhibitors and vaccines.”
Nature calls everyone

It just shouldn’t call so often at night

When your patients wake up to urinate 2 or more times a night, it may be nocturia. In most cases, it’s caused by an overproduction of urine in the kidneys. For millions of patients, it’s a significant bother, and it can lead to health problems that go far beyond interrupted sleep.¹

Learn more at:
www.NatureCalls.us

Can you bill a urethral suspension with radical prostatectomy?

Reporting suspension for patient without pre-op incontinence raises concerns

Q: One of my colleagues tells me that he is billing a urethral suspension at the same time he does his laparoscopic radical prostatectomy and is getting paid by Medicare. That seemed too good to be true since a suspension could be performed on every patient. Is it OK to bill a suspension with a radical prostatectomy?

A: Good question. Unfortunately, it deserves several answers. According to the National Correct Coding Initiative (NCCI), Medicare's bundling edits, the two codes (55866 - Laparoscopy, surgical; nerve sparing, includes robotic assistance, when performed) and 51990 (Laparoscopy, surgical; urethral suspension for stress incontinence) are not bundled and can be charged together without a modifier. However, we have several concerns about billing for the urethral suspension at the same time you perform a radical prostatectomy in a patient who did not have a preoperative incontinence problem necessitating the suspension. First and foremost, by law, Medicare cannot pay for preoperative incontinence that resulted in the determination that the service was not medically necessary at the time the service was performed.

The AUA has also reviewed this issue and indicated in a Policy and Advocacy Brief published May 3, 2017 that reporting the suspension with a prostatectomy should be reserved for those patients with an existing diagnosis of incontinence.

Considering both the current policy interpretation risk and the AUA position, we feel it's important to highlight the concern for future bundling edits. If a high percentage of the radicals are billed with urethral suspension, then it is likely to be bundled in the future and it is possible that it will be tagged with an indicator that will not allow unbundling.

If a high percentage of the radicals are billed with urethral suspension, then it is likely to be bundled in the future and it is possible that it will be tagged with an indicator that will not allow unbundling.

Considering the current policy interpretation risk and the AUA position, we feel it's important to highlight the concern for future bundling edits. If a high percentage of the radicals are billed with urethral suspension, then it is likely to be bundled in the future and it is possible that it will be tagged with an indicator that will not allow unbundling.

Considering this similar situation: Initially, 51800 (Cystoplasty or cystourethroplasty, plastic operation on bladder and/or vesical neck [anterior Y-plasty, vesical fundus resection], any procedure, with or without wedge resection of posterior vesical neck) was not bundled with 55845 (Prostatectomy, retropubic radical, with or without nerve sparing; with bilateral pelvic lymphadenectomy, including external iliac, hypogastric, and obturator nodes), and many physicians were billing the two together. Currently, they are bundled and cannot be unbundled.

In summary, yes, the two procedures can be billed and should be paid. However, we recommend you do not bill, unless the patient has incontinence and the need for the suspension prior to surgery.

Q: My question is about the use of the −59 modifier. I was taught that if two procedures were performed and the bundling edits stated they could be billed with the modifier, you should add the modifier in order to get paid. My understanding from a friend who attended your seminar is that just because the bundling edits indicated you could unbundle with the modifier does not mean that you always should unbundle with a modifier. What is correct?

A: Codes that are included in the NCCI bundling edits with an indicator “1” allow for unbundling if circumstances support that the service is distinct. The computer recognizes that there is special circumstance only if the modifier is appended to the code.

The NCCI is developed using Medicare data with review by a contracted entity. In order to add a modifier to any procedure, the documentation should clearly indicate that the procedure meets the definition of the modifier. Private payers may use modified versions of the NCCI data with additional restrictions or allowances.

The −59 modifier CPT definition is as follows: Distinct Procedural Service: Under certain circumstances, it may be necessary to indicate that a procedure or service was distinct or independent from other non-E/M services performed on the same day. Modifier −59 is used to identify procedures/services, other than E/M services, that are not normally reported together, but are appropriate under the circumstances. Docu-
Offer patients more than a lifetime of pills.

When your patients depend on BPH medications, it can add up to hundreds of pills a year. Quit the bottle and help patients find lasting relief with Rezūm™ Water Vapor Therapy. It treats the problem, not just the symptoms, and gives your patients the freedom they had lost.

**Effective**: 11-point IPSS symptom improvement maintained through 3 years¹

**Durable**: 4.4% procedural retreatment rate at 3 years¹

**Flexible**: Ability to treat all areas of enlarged prostate tissue

**QoL**: Preserves sexual function¹²

**Convenient**: In-office treatment removes the complexities of a hospital setting

---

**Rezūm Water Vapor Therapy**

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

---


Caution: U.S. Federal law restricts this device to sale by or on the order of a physician.

All images are the property of Boston Scientific. All trademarks are the property of their respective owners.

© 2018 Boston Scientific Corporation or its affiliates. All rights reserved. URO-562405-AA AUG 2018
How proposed rule will affect Quality Payment Program

Look for changes to all four Merit-based Incentive Payment System categories

**SUSPENSION** continued from page 18

Medicare does not pay for a different procedure or surgery—this is one of the reasons, therefore, that we recommend that you use the −X (E, S, P, or U) modifiers for Medicare:

- **XE:** Separate encounter
- **XS:** Separate structure/organ
- **XP:** Separate practitioner
- **XU:** Unusual non-overlapping service

As with most coding discussions, it all starts with documentation supporting the services billed. If the operative note does not clearly support one of the definitions above, any denial will be difficult to appeal and once a payer determines that the practice is not appropriately using the modifiers reported, more denials will follow.

Therefore, in our seminars we teach that documentation and circumstances noted must drive correct coding. If the second procedure is a component of the first procedure, is performed to facilitate the first procedure, or the documentation does not support one of the five definitions of the circumstances by which it should be used, then you should not charge for the second procedure with a modifier even if it is allowed by the NCCI.

---

As it did in 2018, CMS has changed the rules for MIPS eligibility to require a minimum threshold of services (200, new) as well as charges ($90,000, unchanged) and patients (200, unchanged). Also, the proposed rule continues to raise the bar for performance in the program. In 2017, clinicians had to achieve a score of 3 to avoid a negative adjustment. In 2018, that threshold was raised to 15, and the 2019 proposed rule calls for a threshold of 30. When mature, this threshold will be determined by the actual mean or median score of all participants. Also, CMS has proposed raising the threshold for “exceptional performance,” and sharing in a separate relative distribution of $500 million, in 2019 to 80 from its current level of 70. When mature, this exceptional performance threshold is determined by statute and tied to the mean/median performance.

The proposed rule addresses changes in each category that comprises the MIPS composite score (table). In the Quality category (45% weight, 1-year reporting period) the proposed rule outlines significant changes, August 2018, page 26.

In this article, I address proposed changes to the Quality Payment Program (QPP) that may impact urology as well as other important details in the rule.

**Rules of eligibility changing**

By now, many urologists have received their Merit-based Incentive Payment System (MIPS) performance feedback report for 2017, and understand that the implementation of the QPP is fully underway. The composite score achieved in 2017 and relative position compared to performance of all other MIPS-eligible clinicians determine how your Medicare payments for professional services in 2019 will be adjusted. The legislation underpinning the creation of MIPS and QPP, and subsequent laws, call for continued implementation, and the proposed rule contains important changes.

As it did in 2018, CMS has changed the rules for eligibility to require a minimum threshold of services (200, new) as well as charges ($90,000, unchanged) and patients (200, unchanged). Clinicians who exceed all three of these thresholds will automatically participate in MIPS, and those who do not meet any cannot participate; those who exceed one or two criteria can opt into the program.

The impact of this change in urology is two-fold: First, there will likely be fewer total eligible clinicians in the program, leading to more competition for fewer program dollars (CMS estimates $372 million will be redistributed). Second, advanced practice providers in a urology practice who bill under their own national provider identifier may not exceed all three thresholds. The latter impact may be a factor in deciding to participate as a group, rather than an individual, especially in the early years of a program when positive payment adjustments are more achievable.

---

**ROBERT A. DOWLING, MD**

Dr. Dowling is the president of Dowling Medical Director Services, a private health care consulting firm specializing in quality improvement, clinical informatics, and health care policy affecting specialty care. He is the former medical director of a large, metropolitan single-specialty urology group in Ft. Worth, TX.
To learn how you can integrate SpaceOAR hydrogel into your urology practice, go to www.spaceoar.com/aua

1. From 3 months onward post radiotherapy (data on file)

CPT is a registered trademark of the American Medical Association
© Augmenix, Inc. All rights reserved. Augmenix, SpaceOAR and SpaceOAR logo are registered trademarks of Augmenix, Inc.
rule adds 10 new MIPS quality measures, most of which do not directly impact the specialty of urology. One of the new measures, Ischemic Vascular Disease Use of Aspirin or Anti-platelet Medication, is actually a replacement of a commonly used MIPS measure (CMS 204) that is being removed. The Urology Specialty set of MIPS measures had one measure removed (Urinary Incontinence: Percentage of female patients aged 65 years and older who were assessed for the presence or absence of urinary incontinence within 12 months) and one outcome measure added (International Prostate Symptom Score: Percentage of patients with an office visit within the measurement period and with a new diagnosis of clinically significant Benign Prostatic Hyperplasia who have International Prostate Symptoms Score (IPSS) or American Urological Association [AUA] Symptom Index [SI] documented at time of diagnosis and again 6 to 12 months later with an improvement of 3 points). The latter measure can be reported via EHR (eCQM specifications), and there were no other significant changes in the submission method for the measures in this set.

CMS has proposed that the Cost category (15% weight, 1-year reporting period [reporting done by CMS]) in 2019 include the two existing measures—Total Per Capita Cost and Medicare Spending Per Beneficiary—as well as eight episode-based measures. None of the eight measures proposed for 2019 involve urologic diagnoses or procedures, but you may expect procedure-based urology episodes in future years.

The Promoting Interoperability category (25% weight, 90-day reporting period) includes significant proposed changes. CMS is proposing to eliminate the concept of a “base score” and instead have each individual measure scored on performance. Unchanged is the requirement to use 2015 certified EHR technology in 2019. There are fewer measures (five) in 2019, including the elimination of Patient-Specific Education, secure messaging, and “view, download, transmit.” Finally, the proposed scoring would award bonus points in 2019 for querying a prescription drug monitoring program and verifying opioid treatment.

The Improvement Activities category (15% weight, 90-day reporting period) contains no significant proposed changes to the inventory of activities for the specialty of urology, and the activity weights (high, medium) and scores remain the same. However, the bonus for using certified EHR technology associated with some activities has been eliminated to align with the proposed changes for promoting interoperability mentioned above.

As mentioned, in this rule CMS has proposed a very significant change to reimburse evaluation/management codes at a single, blended rate (for levels 2-5). To support this change, CMS has also proposed flexibility in documentation—including an option to simply document medical necessity and those items needed for a level 2 visit regardless of the level billed. These proposed changes could significantly reduce the amount of time spent by providers and their staff documenting in the EHR; if finalized, these changes could also result in significant modifications of workflow in the EHR, content redesign, and even changes to the engines that help calculate visit levels. Finally, these changes could change the scope and content of Medicare audits and review activities.

Appropriate use criteria update

The proposed rule continues the implementation of regulations concerning appropriate use criteria (“How will regulatory changes affect EHR use in your practice?” June 2018, page 30). The implementation date has not changed; by Jan. 1, 2020, ordering providers must consult a clinical decision support mechanism prior to ordering advanced imaging. CMS has proposed that this consultation may be performed by a qualified clinical staff member on behalf of the ordering provider—good news for busy urologists. CMS has also clarified in this proposal that the proof of consultation must accompany all claims related to the advanced imaging service; for example, if a urology practice billed the technical component of a computed tomography scan and the contracted radiology group billed the professional service, both claims would need to include the required G codes and modifiers after Jan. 1, 2020 in order to be processed.

Bottom line: The Medicare physician payment policies now include much more than just a fee schedule, and urologists need to understand the proposed changes—good and bad—that could impact their practice.
How can rising interest rates affect your bond portfolio?

Selling a bond prior to maturity may require offering a discount

Q: Should I still hold bonds in my portfolio while there continues to be talk of the Fed raising interest rates?
A: In June the Federal Reserve, commonly referred to as the Fed, raised interest rates for the second time in 2018. During the announcement, the Fed also indicated rates may rise another two times before the year is over. While generally a signal that the economy is strengthening, it also means that rates on credit cards, home equity loans, and other types of borrowing will increase.

Changes in interest rates don’t affect all bonds equally either. Generally speaking, the longer the bond’s maturity, the more it’s affected by changing interest rates. For example, a bond that matures in 20 years will usually lose more of its value if rates go up than another bond that matures in 3 years.

Whether you own individual bonds or bond funds, rising interest rates could create some short-term difficulties. If an individual bond needs to be sold to increase cash flow or provide retirement income, it may need to be sold at a discount to attract a timely buyer. If you have bond funds, the short-term total return may be reduced. If you rely on payouts from these funds to supply your retirement income, you may need to replace the lost income from other sources.

Overall, bonds and bond funds remain an important investment asset and an integral part of a well-diversified portfolio. However, now may be a good time to speak with your financial adviser to discuss the role bonds play in your portfolio and if any changes should be made.

Q: How often should I be speaking with my financial adviser?
A: Many advisers like to speak with their clients every financial quarter. This is a good time to discuss changes that may have occurred over the last 3 months in your personal life, stay up to date on the performance of your accounts, and discuss planning needs that you foresee in the near future. At a minimum, it is important to speak with your financial adviser once a year. They need to remain updated on changes in your life so they can evaluate whether your current wealth management strategy is still appropriate for your circumstances. They are there to be a resource for you. Take advantage of their expertise.

FINANCIAL TIPS
- Individual bonds, bond mutual funds, and exchange-traded funds react differently to rising interest rates.
- Changes in interest rates don’t affect all bonds equally. Generally speaking, the longer the bond’s maturity, the more it’s affected by changing interest rates.
- At a minimum, it is important to speak with your financial adviser once a year.

Mr. Witz is educational program director at MEDIQUIS Asset Advisors, Inc. in Chicago. He welcomes readers’ questions and can be reached at 800-883-8555 or witz@mediquis.com.
**Indication and Important Safety Information**

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

**Important Safety Information**

**Warnings and Precautions**

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

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

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

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

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

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

**Adverse Reactions**

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

**Nonmetastatic CRPC:**
Median metastasis-free survival was 3 years (36.6 months [95% CI, 33.1-119.8] with XTANDI + LHRH therapy† vs 14.7 months [95% CI, 14.2-15.0] with placebo + LHRH therapy† [HR = 0.29 [95% CI, 0.24-0.35]; P < 0.0001]†
- As seen in the PROSPER trial: a multinational, randomized, double-blind phase 3 trial that enrolled 1419 patients with nonmetastatic CRPC who progressed on LHRH therapy.† Eligibility criteria included PSA doubling time ≤ 10 months and no prior chemotherapy‡

**Metastatic CRPC:**
23% reduction in the risk of death with XTANDI + LHRH therapy† vs placebo + LHRH therapy† (HR = 0.77 [95% CI, 0.67-0.88]) and 83% reduction in the risk of radiographic progression or death vs placebo + LHRH therapy† (HR = 0.17 [95% CI, 0.14-0.21]; P < 0.0001)†
- As seen in the PREVAIL trial: a multinational, randomized, double-blind phase 3 trial that enrolled 1717 patients with metastatic CRPC who progressed on LHRH therapy.‡ Eligibility criteria included no prior chemotherapy†

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

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

were asthenia/fatigue, back pain, musculoskeletal pain, hot flush, hypertension, nausea, constipation, diarrhea, upper respiratory tract infection, and weight loss.

In the placebo-controlled study of metastatic CRPC (mCRPC) patients taking XTANDI who previously received docetaxel, Grade 3 and higher adverse reactions were reported among 47% of XTANDI patients and 53% of placebo patients. Discontinuations due to adverse events were reported for 16% of XTANDI patients and 18% of placebo patients. In the placebo-controlled study of chemotherapy-naïve mCRPC patients, Grade 3-4 adverse reactions were reported in 44% of XTANDI patients and 37% of placebo patients. Discontinuations due to adverse events were reported for 6% of both study groups. In the placebo-controlled study of non-metastatic CRPC (nmCRPC) patients, Grade 3 or higher adverse reactions were reported in 31% of XTANDI patients and 23% of placebo patients. Discontinuations due to adverse events were reported for 9% of XTANDI patients and 6% of placebo patients. In the bicalutamide-controlled study of chemotherapy-naïve mCRPC patients, Grade 3-4 adverse reactions were reported in 39% of XTANDI patients and 38% of bicalutamide patients. Discontinuations with an AE as the primary reason were reported for 8% of XTANDI patients and 6% of bicalutamide patients.

**Lab Abnormalities:**
In the two placebo-controlled trials in patients with mCRPC, grade 1-4 neutropenia occurred in 15% of XTANDI patients (1% Grade 3-4) and 6% of placebo patients (0.5% Grade 3-4). In the placebo-controlled trial in patients with nmCRPC, Grade 1-4 neutropenia occurred in 8% of patients receiving XTANDI (0.5% Grade 3-4) and in 5% of patients receiving placebo (0.2% Grade 3-4).

**Hypertension:**
In the two placebo-controlled trials in patients with mCRPC, hypertension was reported in 11% of XTANDI patients and 4% of placebo patients. Hypertension led to study discontinuation in < 1% of patients in each arm. In the placebo-controlled trial in patients with nmCRPC, hypertension was reported in 12% of patients receiving XTANDI and 5% of patients receiving placebo.

**Drug Interactions**

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

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

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

**References:**
**XTANDI® (enzalutamide) capsules for oral use**

**Initial U.S. Approval: 2012**

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

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

**INDICATIONS AND USAGE**

XTANDI is an androgen receptor inhibitor indicated for the treatment of patients with castration-resistant prostate cancer.

**CONTRAINDICATIONS**

None.

**WARNINGS AND PRECAUTIONS**

Seizure

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

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

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

**Posterior Reversible Encephalopathy Syndrome (PRES)**

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

**Hypersensitivity**

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

Permanently discontinue XTANDI for serious hypersensitivity reactions.

**Ischemic Heart Disease**

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

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

**Falls and Fractures**

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

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

**Embryo-Fetal Toxicity**

The safety and efficacy of XTANDI have not been established in females. Based on animal reproductive studies and mechanism of action, XTANDI can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment with XTANDI. XTANDI should not be handled by females who are or may become pregnant.

**ADVERSE REACTIONS**

**Clinical Trial Experience**

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

Four randomized controlled clinical trials enrolled patients with CRPC who had progressed on androgen deprivation therapy ( GnRH therapy or prior bilateral orchectomy). Three trials were placebo-controlled and one trial was bicalutamide-controlled. Patients received XTANDI 160 mg (2784 patients) or placebo orally once daily (1708 patients) or bicalutamide 50 mg orally once daily (189 patients). All patients continued androgen deprivation therapy (ADT).

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

**AFFIRM (NCT00874311): XTANDI versus Placebo in Metastatic CRPC Following Chemotherapy**

AFFIRM enrolled 1199 patients with metastatic CRPC who had previously received docetaxel. The median duration of treatment was 8.3 months with XTANDI and 3.0 months with placebo. During the trial, 48% of patients on the XTANDI arm and 46% of patients on the placebo arm received glucocorticoids.

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

Table 1. Adverse Reactions in AFFIRM

<table>
<thead>
<tr>
<th></th>
<th>XTANDI N = 800</th>
<th>Placebo N = 389</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3-4 (%)</td>
<td>Grade 3-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenic Conditions</td>
<td>51</td>
<td>9.0</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>15</td>
<td>1.0</td>
</tr>
<tr>
<td>Musculo-skeletal Pain</td>
<td>15</td>
<td>1.3</td>
</tr>
<tr>
<td>Muscular Weakness</td>
<td>9.9</td>
<td>1.5</td>
</tr>
<tr>
<td>Edema</td>
<td>2.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22</td>
<td>1.1</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot Flush</td>
<td>20</td>
<td>0.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6.4</td>
<td>2.1</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>6.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>4.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypotension</td>
<td>4.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>11</td>
<td>0.0</td>
</tr>
<tr>
<td>Lower Respiratory Tract and Lung Infection</td>
<td>8.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>8.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Anxiety</td>
<td>6.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td>6.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Pollakiuria</td>
<td>4.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Infectious and Procedural Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>4.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>3.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Respiratory Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>3.3</td>
<td>0.1</td>
</tr>
</tbody>
</table>

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

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

Table 2. Adverse Reactions in PREVAIL

<table>
<thead>
<tr>
<th>Event</th>
<th>XTANDI Grade 1-4 (%)</th>
<th>Placebo Grade 1-4 (%)</th>
<th>XTANDI Grade 3-4 (%)</th>
<th>Placebo Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenic Conditions</td>
<td>47.3</td>
<td>33.2</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>12.0</td>
<td>8.2</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back Pain</td>
<td>29.5</td>
<td>22.6</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>21.6</td>
<td>16.1</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>23.7</td>
<td>17.4</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17.3</td>
<td>13.2</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot Flush</td>
<td>18.1</td>
<td>7.8</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>14.7</td>
<td>4.1</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>11.3</td>
<td>7.1</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>11.2</td>
<td>7.0</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Dysuria</td>
<td>7.6</td>
<td>3.7</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Mental Impairment Disorders</td>
<td>5.7</td>
<td>0.0</td>
<td>1.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Restless Legs Syndrome</td>
<td>2.1</td>
<td>0.1</td>
<td>0.4</td>
<td>0.0</td>
</tr>
<tr>
<td>Respiratory Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>11.6</td>
<td>6.5</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>16.0</td>
<td>11.0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Lower Respiratory Tract and Lung Infection</td>
<td>7.9</td>
<td>15.4</td>
<td>4.7</td>
<td>1.1</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>8.2</td>
<td>0.1</td>
<td>5.7</td>
<td>0.0</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td>8.8</td>
<td>1.3</td>
<td>5.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Injury, Poisoning and Procedural Complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>13.6</td>
<td>5.3</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Non-Pathological Fracture</td>
<td>8.8</td>
<td>2.1</td>
<td>3.0</td>
<td>1.1</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>19.3</td>
<td>0.3</td>
<td>16.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Weight Decreased</td>
<td>12.0</td>
<td>8.5</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Reproductive System and Breast Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>3.4</td>
<td>0.0</td>
<td>1.4</td>
<td>0.0</td>
</tr>
</tbody>
</table>

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

PROSPER enrolled 1401 patients with non-metastatic CRPC, of whom 1395 received at least one dose of study drug. Patients were randomized 2:1 and received either XTANDI at a dose of 160 mg once daily (N = 930) or placebo (N = 465). The median duration of treatment at the time of analysis was 18.4 months (range: 0.0 to 42 months) with XTANDI and 11.1 months (range: 0.0 to 43 months) with placebo. Overall, 32 patients (3.4%) receiving XTANDI died with placebo.

Table 4. Laboratory Abnormalities in PROSPER

<table>
<thead>
<tr>
<th>Event</th>
<th>XTANDI Grade 1-4 (%)</th>
<th>Placebo Grade 1-4 (%)</th>
<th>XTANDI Grade 3-4 (%)</th>
<th>Placebo Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>8.2</td>
<td>0.5</td>
<td>5.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Hypoanemia</td>
<td>16.1</td>
<td>8.8</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>78.7</td>
<td>2.9</td>
<td>73.1</td>
<td>1.3</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>26.0</td>
<td>21.0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Laboratory Abnormalities in the AFFIRM and PREVAIL studies in metastatic CRPC, Grade 1-4 neutropenia occurred in 15% of patients receiving XTANDI (1% Grade 3-4) and in 6% of patients receiving placebo (0.5% Grade 3-4).

Table 5. Laboratory Abnormalities in PROSPER

<table>
<thead>
<tr>
<th>Event</th>
<th>XTANDI Grade 1-4 (%)</th>
<th>Placebo Grade 1-4 (%)</th>
<th>XTANDI Grade 3-4 (%)</th>
<th>Placebo Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>8.2</td>
<td>0.5</td>
<td>5.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Hypoanemia</td>
<td>16.1</td>
<td>8.8</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>78.7</td>
<td>2.9</td>
<td>73.1</td>
<td>1.3</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>26.0</td>
<td>21.0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
Hypertension
In the AFFIRM and PREVAIL studies in metastatic CRPC, hypertension was reported in 11% of patients receiving XTANDI and 4% of patients receiving placebo. Medical history of hypertension was balanced between arms. Hypertension led to study discontinuation in 1% of patients in each arm in the PROSPER study in non-metastatic CRPC, hypertension was reported in 12% of patients receiving XTANDI and 5% of patients receiving placebo.

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

Body as a Whole: hypersensitivity (edema of the face, tongue, lip, or pharynx)
Gastrointestinal Disorders: vomiting
Neurological Disorders: posterior reversible encephalopathy syndrome (PRES)
Skin and Subcutaneous Tissue Disorders: rash

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

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

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

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary
The safety and efficacy of XTANDI have not been established in females. Based on animal reproductive studies and mechanism of action, XTANDI can cause fetal harm and loss of pregnancy. There are no human data on the use of XTANDI in pregnant females. Based on nonclinical findings in repeat-dose toxicity studies, which were consistent with the pharmacological activity of enzalutamide, male fertility may be impaired by treatment with XTANDI. In a 26-week study in rats, atrophy of the prostate and seminal vesicles was observed at doses up to 20 mg/kg/day. Enzalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either the in vitro mouse lymphoma thymidine kinase (TK) gene mutation assay or the in vivo mouse micronucleus assay.

Based on nonclinical findings in repeat-dose toxicity studies, which were consistent with the pharmacological activity of enzalutamide, male fertility may be impaired by treatment with XTANDI. In a 26-week study in rats, atrophy of the prostate and seminal vesicles was observed at doses up to 20 mg/kg/day (equal to the human exposure based on AUC). In 4-, 13-, and 39-week studies in dogs, hypospermogenesia and atrophy of the prostate and epididymides were observed at ≥ 4 mg/kg/day (0.3 times the human exposure based on AUC).

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Administration of enzalutamide to male and female rhesus transgenic mice by oral gavage daily for 26 weeks did not result in increased incidence of neoplasms at doses up to 20 mg/kg/day.

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

Manufactured for and Distributed by: Astellas Pharma US, Inc., Northbrook, IL 60062
Marketed by: Astellas Pharma US, Inc., Northbrook, IL 60062
Pfizer Inc., New York, NY 10017
Revised: July 2018
198511-XTA-USA
Rx Only
© 2018 Astellas Pharma US, Inc.
XTANDI® is a registered trademark of Astellas Pharma Inc.
APPs continued from page 1

APP work force. About 28% of all specialty practices employed APPs in 2016, according to a recent research letter published in *JAMA Internal Medicine* (2018; 178:988-90). That’s a 22% jump from the percentage of specialty practices employing APPs in 2008.

**APPs’ expanding roles**
The AUA’s position is that APPs should prac-
tice as a team with a board-certified urologist as the head of that team, according to Christopher Gonzalez, MD, MBA, professor and chair of urology at Loyola University School of Medicine, Chicago. Dr. Gonzalez led an AUA working group, including APPs, to develop the AUA Consensus Statement on Advanced Practice Providers, published in 2013.

That position hasn’t changed since 2013, but the roles that APPs have within those teams appear to be expanding. One example: surgery. Urologists are increasingly using APPs as assistants in surgery, particularly in robotic and laparoscopic operations, Dr. Erickson and colleagues reported in a 2017 study (*Urology* 2017; 106:76-81). The most common way in which APPs assist urologists in clinical procedures is in the operating room (30%), according to the 2017 AUA Census. APPs also assist with cystoscopy for difficult catheter placement, cystoscopy for diagnostic or cancer surveillance, urodynamics interpretation, cystoscopy for stent removal, cystoscopy for botulinum injections, cystoscopy for bladder biopsy, circumcision, vasectomy, and priapism injection treatment, according to AUA data, which was presented in part by Raymond Fang et al at the AUA annual meeting in San Francisco.

More controversial is the fact that APPs increasingly perform some urologic procedures independently. The AUA reports that the most common clinical procedures APPs performed independently in 2017 were bladder instillation (56.3%) and intracavernosal injections for erectile dysfunction (55%). About 40% of APPs perform urodynamics interpretation independently, 39% do percutaneous tibial nerve stimulation, and 33.8% do chemotherapy injections. More than one-fourth of APPs administer luteinizing hormone-releasing hormone antagonists and conduct urodynamics.

Approximately one-fourth of APPs independently perform cystoscopy for stent removal, neuromodulation with InterStim programming, and priapism injection treatments.

Dr. Erickson and colleagues authored a study published March 2017 in *Urology Practice* that found APPs independently performed 54,549 simple procedures in urologic practice in 2003 versus 230,683 such procedures, including post-void residual, insertion of catheter and interpretation of uroflowmetry, in 2014. APPs independently billed for 328 cystoscopies in 2003 compared to 2,284 in 2014 (*Urol Pract* 2017; 4:169–75).

Research looking at whether APPs perform urologic procedures like these as safely and effectively as urologists is lacking, according to Dr. Gonzalez. “We just know that the trends show a small number of more complex procedures are being done by advanced practice providers and that number of procedures is starting to grow,” he said.

While most procedures that APPs are performing are relatively straightforward, some are complex with notable technique-based side effect profiles, according to urologist J. Stuart Wolf, Jr., MD, professor in the department of surgery and perioperative care, Dell Medical School, University of Texas at Austin.

“The important issue when you’re having an advanced practice provider do a procedure is not only making sure they have the technical skills to do the procedure but also that they know when something’s wrong, when something’s different and out of the ordinary, and when to involve the supervising physician,” Dr. Wolf said. “I think cystoscopy for bladder tumor surveillance is a great example. Sure, technically it’s not a whole lot different than doing cystoscopy for stent removal. But cognitively, it’s significantly different. It entails a lot more knowledge to do well.”

**What urologists need to know about APPs and profitability**

Many urologists are concerned about cost and profitability when they consider adding APPs to their practice, Christopher Gonzalez, MD, MBA, said.

He and colleagues have done studies looking at what it takes to make adding APPs in academia and hospital settings profitable. They’ve found that the benchmark for an APP to be profitable is if they work roughly 3,000 work relative value units (wRVUs) annually.

“In the private sector it’s probably a little different,” Dr. Gonzalez said.

In general, most APPs collect about 85% of what a urologist would bill for. And if the urologist sees a patient once and then the APP engages in the care of that patient, then the practice can get 100% of the charges, Dr. Gonzalez explained.

One caveat is that APPs don’t generally come out of training with urology-specific experience, according to Dr. Gonzalez.

“The practice has to train them. There is going to be cost for the first 6 to 12 months to train them, when the practice won’t be able to generate the revenue. But usually after the first year, they’re able to generate revenue,” he said.

**“To manage all [of patients’] medical needs, especially the chronic diseases, we’ll need to continue to see evolution in the urologist/APP partnership.”**

BRADLEY A. ERICKSON, MD, MS

Please see APPs, on page 30
“I think that’s a good example of a procedure that perhaps a well-trained APP could do under supervision with the attending looking at the monitor, although frankly, I would argue at that point you’re better off just having the physician doing the procedure.”

Dr. Wolf, who works with a physician assistant in his practice, said it’s important to teach APPs the cognitive aspect of procedures—knowing when to do something, when not to do something, and when to change course. He said urologists’ concerns about working with APPs are less about turf and more about patient safety and outcomes.

“It really gets down to a quality of care issue,” he said. “If an APP can do tasks to free me to do more complex tasks, that’s good for quality of care. The only time I get worried is if the practice of the APP creeps into those more complex areas where more subject matter expertise is required. Then quality might suffer.”

Improving access

APPs can increase patient access, and that’s a big deal and real need in urology, experts in the field say.

Barry Kogan, MD, chief of urology at Albany Medical College, Albany, NY, said having an APP in his pediatric urology practice helps him accomplish things he might not have the time or patience for.

“We treat bedwetting, and that’s a problem that takes a lot of time and effort. As someone who is more focused on surgery, maybe I have less time to take with families, whereas my nurse practitioner is more able to discuss the issues in more depth with families,” Dr. Kogan said. “I can only see so many patients. APPs help with access.”

Maximize Your Reimbursement

2019 Urology Advanced Coding and Reimbursement Seminar

Significant Changes to 2019 E/M Rules Proposed
Join us, learn the new rules, and be prepared!

Early Bird Registration Open

Date: November 30 - December 1, 2018
Location: Bally’s Las Vegas Hotel & Casino

To Register:
http://prsnetwork.com/uacrs
info@prsnetwork.com (800) 972 - 9298

REPORT: UROLOGY PAs EARN $105K, WORK 42 HOURS/WEEK

Certified physician assistants (PAs) are heavily integrated on health care teams in urology and virtually every other specialty, according to the 2017 Statistical Report of Certified Physician Assistants by Specialty.

The percentage of PAs working in surgical subspecialties increased over 70% since 2013, according to the report, issued in July 2018 by the National Commission on Certification of Physician Assistants, Inc. The statistics, the commission says, also seem to indicate that PAs are filling the physician shortage gap, especially in non-primary care specialties.

Key urology-specific findings of the report include:

- The mean income of certified PAs in urology is $104,742. About 38% earn $100,001 to $120,000, and 31% earn $80,001 to $100,000.
- Urology PAs work a mean of 42.3 hours per week at their principal clinical position. Among those working at least 40 hours per week, they see a mean of 74 patients in a typical week.
- Among the services urology PAs provide in their principal clinical position, 88% conduct physical examinations and obtain medical histories for “most patients.” They also commonly order, perform, and interpret lab tests, X-rays, EKGs, and other diagnostic studies (84%); prescribe medications for acute and chronic illnesses (84%); counsel and educate patients and families (78%); and provide diagnosis, treatment, and management of chronic (69%) and acute illnesses (66%).
- Over half (56%) of PAs in urology work in an office-based, private practice setting. One-third work in a hospital, 8% work in a federal government facility/hospital/unit, and just over 1% work in a school or college-based health center or school clinic.

The full report can be viewed at www.nccpa.net/research.
THE PA PERSPECTIVE ON PERFORMING PROCEDURES AND MORE

In this Urology Times Q&A, Jessica Nelson, MPAS, PA-C, past president of the Urological Association of Physician Assistants (UAPA), offers a physician assistant’s perspective on PAs performing urologic procedures, PA training, and more. Nelson works in the department of urology at UT Southwestern Medical Center in Dallas. She was interviewed by Urology Times Correspondent Lisette Hilton.

What is UAPA’s position on the use of PAs performing urologic procedures?
Currently the board has not taken a stand or published a formal statement regarding PAs performing urologic procedures. PAs legally function under the delegatory authority of physicians. Therefore, PAs can perform procedures within their training and scope of practice if delegated by a physician.

UAPA members are known to perform cystoscopy (diagnostic, therapeutic, catheter placement, and stent removal); hormone pellet insertions; intracavernosal injections and irrigations; transrectal ultrasound, with or without prostate biopsy; posterior tibial nerve stimulation; bladder Botox injections; circumcision; vasectomy; and first assisting in surgery. UAPA would encourage PA-physician teams to practice in accordance with state law and for the physician to delegate activities that are in their scope of practice and can be safely delegated as determined by the skill of the PA.

Is there interest among urology PAs in practicing independently from urologists?
PAs have never described the goal of the profession to “practice independently” of a physician. In May 2017, the American Academy of Physician Assistants published a policy change describing Optimal Team Practice (www.aapa.org/optimal-team-practice), and the policy emphasizes the PA’s commitment to team practice. UAPA supports the call for physicians and PAs to make practice-level decisions to improve patient access to care and to optimize patient outcomes in light of the challenges facing the specialty regarding adequate workforce.

What do you think urologists might not know about PA training?
PA education is rigorous and the average program length is 28 months. All programs (currently 236) are accredited by the Accreditation Review Commission on Education for the Physician Assistant. Our education is modeled on the medical school curriculum with both pre-clinical instruction and clinical rotations. There are seven required rotations in family practice, internal medicine, women’s health, mental health, pediatrics, general surgery, and emergency medicine, with medicine and surgery elective rotations offered. The mean number of clinical contact hours is 1,993 hours spaced over an average of 51.2 weeks, according to the last Physician Assistant Education Association curriculum survey.

All graduate PAs must sit and pass the Physician Assistant National Certification Exam in order to become licensed in any of the 30 states. Lastly, multiple studies have shown that PAs add value to health care teams, provide excellent patient care, and are accepted by the patients they serve.

What is one tip that you think would help urologists better utilize advanced practice providers?
The PA profession does not use the term advanced practice provider to describe the profession and my comments are directed to how urologists can best utilize PAs on the health care team. There is no prescribed standard for which PAs gain urology-specific training. There are some postgraduate programs, which provide vast knowledge and experience, but there are not enough to meet the need and fellowship training is not for everyone. With that said, I would recommend investing the first several weeks, even months of a new PA’s onboarding in urology to be spent side by side with the physician, so they learn not only about urology but also certain practice preferences and standards of patient care. Teach them how to perform procedures, encourage them to read/attend journal clubs or grand rounds if that is an option.

And finally, mentoring is an important component of long-term physician-PA partnership. Of course, encourage their attendance at our annual UAPA conference, which is specifically geared toward PAs and advanced practice nurses in urology, providing both didactic lectures and hands on skills.

To conclude, there are numerous benefits of using PAs to their full scope of practice. They include: increased appointment availability with more timely access to care for patients, increasing workflow efficiency and coordination of care, management of non-surgical patient and those with chronic urologic diseases, care coordination for postoperative patients (for instance post-prostatectomy patients regarding incontinence and sexual function rehabilitation), follow-up care and cancer survivorship programs for oncology patients, and participation in clinical trial research.
APPs might be a solution for increasing access problems due to an aging urologist workforce. Twenty-seven percent of practicing urologists plan to retire in the next 5 years. Compared to non-retiring urologists, those near retirement are more likely to practice outside metropolitan areas, a study based on AUA Census data found (Urology 2016; 94:85-9).

“There’s a concern that we won’t have enough providers or we’ll have a geographic maldistribution of providers, where younger urologists and large groups will be concentrated in urban areas and rural areas will be underserved,” Dr. Gonzalez said. “This is where we really think there’s an opportunity with advanced practice providers.”

The number of urologic providers probably will be adequate if some of the nonsurgical care is directed elsewhere, according to Dr. Erickson.

“The only time I get worried is if the practice of the APP creeps into those more complex areas where more subject matter expertise is required. Then quality might suffer.”

J. STUART WOLF, JR., MD

“I think that we’ll probably be OK with the current workforce if we’re just concerned about the surgical needs of our patients. However, to manage all their medical needs, especially the chronic diseases, we’ll need to continue to see evolution in the urologist/APP partnership,” Dr. Erickson said.

There’s a natural tendency for urologists to treat APPs as second-class citizens, Dr. Kogan said. “I think treating them with courtesy and respect and understanding that they bring something to the table is really important,” he said. “Once they’re up to speed and educated, then I think you want to treat them as a full partner on the team and let them know that.”

Karla Giramonti, MS, FNP-BC, of Albany Medical Center’s division of urology, works with Dr. Kogan. She said the two things that have most helped her in practice have been the practice’s team approach to patient care and Dr. Kogan’s continuous teaching. Today, Giramonti performs circumcisions in the operating room and in the office.

“That’s something many surgeons consider a fairly minor procedure, but in New York it’s a very much needed procedure. It saves the operating room time for Dr. Kogan to do cases that are much more serious and need to be done in a timely manner,” Giramonti said. “Dr. Kogan is constantly training me and I’m constantly learning. We did the circumcisions together. We confirmed that I had my knowledge base that was well documented. He makes himself available if there’s a concern. He makes sure that I’m comfortable.”

To optimize their relationships with APPs in practice, urologists should allow APPs to participate in practice decisions, she said. “I think that allowing them to be a true partner on the team and let them know that.”

APP training 101

APP training in urology can come from within the practice. There are also some programs around the U.S. that train nurse practitioners, physician assistants, or both in urology practice, including those at Mayo Clinic, UT Southwestern, Rosalind Franklin University, University of Southern California, Vanderbilt, and the Carolina Medical Centers in Charlotte, NC.

The AUA also offers programs that are helpful to APPs in urologic practice, according to Heather Schultz, NP, chair of the AUA’s APP Education Committee. Education opportunities for APPs include:

- A part of AUA member benefits, APPs and allied health professionals have access to Urology Place, which is a platform for those working in urology to connect, discuss and share information.
- The Urology Care Foundation offers free, printable patient education materials.
- The AUA offers online education modules for APPs, where they can obtain continuing education credit through AUA University.
- The Society of Urologic Nurse and Associates offers regional and national meetings, online education, publications and urology certification through the Certification Board for Urology Nurses and Associates.
- The Urological Association of Physician Assistants offers national meetings, online education, and publications.
- The AUA also offers guidelines, white papers, and best practice statements, which can help APPs in practice.

At the annual AUA meeting, free with registration, there is a two-day program for APPs on a variety of topics based on past years evaluations and education needs assessment surveys.

THE AUA ALSO OFFERS PROGRAMS THAT ARE HELPFUL TO APPS IN UROLOGIC PRACTICE, ACCORDING TO HEATHER SCHULZ, NP, CHAIR OF THE AUA’S APP EDUCATION COMMITTEE. EDUCATION OPPORTUNITIES FOR APPS INCLUDE:

- A PART OF AUA MEMBER BENEFITS, APPS AND ALLIED HEALTH PROFESSIONALS HAVE ACCESS TO UROLOGY PLACE, WHICH IS A PLATFORM FOR THOSE WORKING IN UROLOGY TO CONNECT, DISCUSS AND SHARE INFORMATION.
- THE UROLOGY CARE FOUNDATION OFFERS FREE, PRINTABLE PATIENT EDUCATION MATERIALS.
- THE AUA OFFERS ONLINE EDUCATION MODULES FOR APPS, WHERE THEY CAN OBTAIN CONTINUING EDUCATION CREDIT THROUGH AUA UNIVERSITY.
- THE SOCIETY OF UROLOGIC NURSE AND ASSOCIATES OFFERS REGIONAL AND NATIONAL MEETINGS, ONLINE EDUCATION, PUBLICATIONS AND UROLOGY CERTIFICATION THROUGH THE CERTIFICATION BOARD FOR UROLOGY NURSES AND ASSOCIATES.
- THE UROLOGICAL ASSOCIATION OF PHYSICIAN ASSISTANTS OFFERS NATIONAL MEETINGS, ONLINE EDUCATION, AND PUBLICATIONS.
- THE AUA ALSO OFFERS GUIDELINES, WHITE PAPERS, AND BEST PRACTICE STATEMENTS, WHICH CAN HELP APPS IN PRACTICE.

The number of urologic providers probably will be adequate if some of the nonsurgical care is directed elsewhere, according to Dr. Erickson.
How do you counsel patients about at-home genetic tests?

Patients who come in with home genetic test results are clearly concerned about their cancer risks. We need to address that by understanding their family history, whether there are any cancer syndromes in their family, their comorbidities, and their age.

I get a yearly PSA. I would get an MRI to make sure there was no malignancy that had not been detected through PSA.

We’ve started getting MRIs every 3 to 5 years. The goal is to detect the cancer early, but we’re learning the best way to manage these risks.

If a patient is clearly anxious about their genetic predisposition to malignancies, we have genetic counselors who are experts in not only understanding the genetic basis, but also counseling, so patients know their actual risks and how they should act on them.

Patients hear they’re at increased risk of malignancy, but don’t hear the degree of risk. I’ve had patients who were told they had a 15% lifetime risk of prostate cancer and are concerned. I tell them, ‘That’s everybody’s risk.’ They’re not at high risk; that’s average risk.

Those tests are associated with an increased risk of prostate cancer but not necessarily an increased risk of aggressive prostate cancer. That’s the cancer we want to diagnose—not nonaggressive prostate cancer. Are patients at risk for developing cancer when they’re 75, or 55? Our evaluation and management will be different depending on the clinical scenario.

On the horizon, there will be clear genetic tests and we’ll need to design clinical care to alter the identified risks. If we tell patients they have increased risk of disease, but don’t do anything to alter that risk, we have not improved our patients’ lives; we’ve actually made their lives worse.

Adam Kibel, MD / Boston

I just had a middle-aged gentleman, whose wife is a pathologist, come in with a variance of the CHEK2 mutation. The superficial research I did never associated this variant with prostate cancer, but his wife was convinced he had prostate cancer. It turns out his sister had breast cancer and another younger family member had ovarian cancer, so there was already a red flag there might be familial cancer. He had a mildly elevated PSA, and when I did his rectal exam he had a slight abnormality. A transrectal ultrasound-guided biopsy showed he had fairly significant prostate cancer in the majority of the cores I took.

I’ve actually had several cases from home tests this past year—a BRCA1 and a BRCA2 mutation, and a possible ATF mutation. They’re still fairly uncommon, but urologists in practice now need to have at least some working knowledge in this area because I’ve seen it several times in my academic practice. I suspect community urologists will start seeing this periodically.

If a random patient comes in with localized disease, an elevated PSA, no family history, and no metastasis, the chance of finding a mutation in one of these known genes is less than 5%. But if the patient comes in with 23andMe, with some gene mutation or variance, the safest thing is to do the rectal exam, a PSA, and a phi or 4Kscore, to ascertain their risk—maybe even a lower threshold for offering those patients a biopsy.

I’m trying to teach my residents, and myself, to think more about family history, especially where cancers are occurring in younger people.

If the patient has a strong family history, I would at least talk to them. I have a nurse who is trained to talk about genetic testing offered through our cancer center.

Judd Moul, MD / Durham, NC

I haven’t had patients do their own home genetic tests, although they’ve requested genetic tests be done here.

The hospital does genetic screening, and we have a genetics department that consults, especially for patients with multiple malignancies, young people where cancer’s not expected, or people with a strong family history. We’re not testing prostate biopsy samples yet, although I have a feeling that will change soon.

I’m not sure what’s covered by insurance yet. It costs 4 to 5 grand, so people don’t do that very often.

My issue is that the genetic link is usually found after a patient is already diagnosed with cancer. We screen to see if they have something that would make them susceptible to other cancers. Then they are usually passed on for more aggressive screening.

Some patients appreciate those tests, but honestly, I probably have just as many patients not want genetic screening. They don’t want to know.

It hasn’t made a difference in my treatments. I don’t know if we’ve found anybody yet who had any kind of syndrome or that we have to screen for further cancers.”

Ronald Im, MD / Hillsboro, OR

ADVERTISERS INDEX

Companies featured in this issue

To obtain additional information about products advertised in this issue, use the contact information below. This index is provided as an additional service. The publisher does not assume any liability for errors or omissions.

<table>
<thead>
<tr>
<th>Advertiser Name</th>
<th>Brand/Product</th>
<th>Page #</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accurate Surgical &amp; Scientific Instruments</td>
<td>Microspike</td>
<td>7</td>
<td><a href="http://www.accuratesurgical.com">www.accuratesurgical.com</a></td>
</tr>
<tr>
<td>Astellas</td>
<td>XTANDI</td>
<td>Cover tip, 24-28</td>
<td><a href="http://www.xtandhcp.com">www.xtandhcp.com</a></td>
</tr>
<tr>
<td>Augmenix Inc.</td>
<td>SpaceOAR</td>
<td>21</td>
<td><a href="http://www.spaceoar.com">www.spaceoar.com</a></td>
</tr>
<tr>
<td>Avadel Pharmaceuticals</td>
<td>Condition Awareness Campaign</td>
<td>17</td>
<td><a href="http://www.avadel.com">www.avadel.com</a></td>
</tr>
<tr>
<td>Boston Scientific</td>
<td>BSC Urology</td>
<td>CV4</td>
<td>bostonscientific.com/ beyondstents</td>
</tr>
<tr>
<td>MDxHealth Inc.</td>
<td>ConfirmMDx</td>
<td>CV2</td>
<td><a href="http://www.mdxhealth.com">www.mdxhealth.com</a></td>
</tr>
<tr>
<td>NeoTract</td>
<td>UroLift</td>
<td>CV3</td>
<td><a href="http://www.urolift.com">www.urolift.com</a></td>
</tr>
<tr>
<td>NxThera</td>
<td>Rezum</td>
<td>19</td>
<td><a href="http://www.rezum.com">www.rezum.com</a></td>
</tr>
<tr>
<td>Physician Reimbursement Systems</td>
<td>-</td>
<td>30</td>
<td><a href="http://www.prnetwork.com">www.prnetwork.com</a></td>
</tr>
<tr>
<td>Teleflex Medical</td>
<td>Hem-o-lok® Polymer Clip</td>
<td>9</td>
<td><a href="http://www.teleflex.com">www.teleflex.com</a></td>
</tr>
</tbody>
</table>
MEDICAL EQUIPMENT

The Future of Patient Positioning

**Excellent for in-office procedures**

- Cushioned GStirrup® boots provide a safe and comfortable place for patients to rest their feet and legs
- Easily slide onto current footrests on almost any table
- No tools required, installs in seconds
- Helpful for the elderly or patients with neurological disorders
- Qualifies for the Disabled Access Tax Credit of almost 50%

The GStirrup meets US Access Board standards and a tax credit is available when set is purchased under the American Disability Act. Tax form 8826

To order contact your favorite distributor rep. or order direct at 844-587-8719 or www.GStirrup.com

$100 off with coupon Gstirrup2018

---

Content Licensing for Every Marketing Strategy

Marketing solutions fit for:
- Outdoor
- Direct Mail
- Print Advertising
- Tradeshow/POP Displays
- Social Media
- Radio & TV

**Logo Licensing | Reprints | Eprints | Plaques**

Leverage branded content from *Urology Times* to create a more powerful and sophisticated statement about your product, service, or company in your next marketing campaign. Contact Wright’s Media to find out more about how we can customize your acknowledgements and recognitions to enhance your marketing strategies.

For information, call Wright’s Media at 877.652.5295 or visit our website at www.wrightsmedia.com
OHIO

JOIN A SUCCESSFUL, WELL ESTABLISHED MULTI-SPECIALTY GROUP SEEKING TO ADD A FULL-TIME UROLOGIST IN DAYTON, OHIO.

MULTI SPECIALTY GROUP IS SEEKING AN UROLOGIST TO JOIN OUR TEAM TO PROVIDE QUALITY PATIENT CARE IN THE GREATER DAYTON AREA. MULTIPLE LOCATIONS WITH FULL SUPPORT STAFF AND MODERN EQUIPMENT ENSURE A TERRIFIC FUTURE FOR THE SUCCESSFUL CANDIDATE. WE ARE 40+ PHYSICIANS AND 300+ EMPLOYEES. OUR MISSION IS TO EARN THE TRUST OF OUR PATIENTS & COLLEAGUES BY EXCEEDING EXPECTATIONS IN QUALITY OF CARE, SCOPE OF SERVICE AND COMPASSION.

- Collaborate with 10 urologists in a thriving practice
- Friendly, helpful staff
- Clean, spacious work environment
- Established referral base from area doctors

We offer a competitive salary with partnership opportunities. Income based on fees from both the technical and professional components. Practice provides comprehensive benefits including: malpractice, health, life, disability and dental insurance, a generous vacation package, 401(k) retirement plan and paid professional expenses.

Please email CV to: Eric J. Sedwick, MBA, CPC
Call 937-208-2482 • ejsedwick@premierhealth.com

FLORIDA

FLORIDA UROLOGY CENTER
Daytona Beach, FL

Wonderful Climate, Coastal living
Excellent schools, Looking for Board Eligible/Board Certified Urologist.
Beautiful main office of 11,000 sq. ft., with three satellite office locations.
A 12,000 sq. ft. attached Surgery Center, Lithotripsy, Laser, etc.
On site CT, X-ray, Pathology lab. Shared IGRT facility.
One Hospital with paid ER call. Robotics not necessary.

If interested, please call
Lee Baylor, Administrator
at (386) 673-5100
or email fluro@bellsouth.net

NORTH CAROLINA

VIEWMONT UROLOGY CLINIC, PA

Viewmont Urology Clinic, PA is located in Hickory, NC just north of Charlotte.
We are currently searching for a Full Time Urologist to join our Privately Owned 7 physician Urology Clinic. Our mission is to offer patients the highest standards of urological medical care based on mutual understanding, respect, and trust.

Opportunity for partnership after one year of practice, competitive salary, comprehensive benefits package including: malpractice, health, life, disability and dental insurance, 9 weeks of paid vacation, 401(k), and paid professional expenses.

Please send CV’s to: Chris Wayne, Practice Manager
chriswayne@viewmonturology.com

FOR PRODUCTS & SERVICES RECRUITMENT PLEASE CONTACT:

JOANNA SHIPPOLI at
800-225-4569 x 2615 or
E-mail: joanna.shippoli@ubm.com
Improving QOL in Prostate Radiotherapy

*What every urologist needs to know*

Study data has shown that SpaceOAR® hydrogel significantly improves quality of life for patients with prostate cancer who have undergone radiotherapy. But what does it take to implement this procedure into routine practice, and what can urologists expect regarding reimbursement?

In this supplement, practicing urologists will share perspectives on this procedure, addressing topics that include reimbursements, learning curves, clinical implementations, and equipment needs.

read more at urologytimes.com/spaceoar
Specialties to Congress: Don’t ditch MIPS

AUA advocates for this, other issues during ‘fly-in’

Congress has been urged to reject a proposal by the Medicare Payment Advisory Commission to ditch the fledgling Merit-based Incentive Payment System (MIPS) quality program that was established in 2015 as part of a plan to replace an outdated physician payment system that annually threatened deep cuts in provider payments.

In testimony before the House Energy and Commerce Committee’s Health Subcommittee July 26, ophthalmologist Parag Parekh, MD, representing the Alliance of Specialty Medicine, said the MIPS program “provides the only mechanism for many specialists and subspecialists to engage in federally-sponsored quality improvement and demonstrate their commitment to deliver high-value care.”

The hearing on MIPS came just a week after 11 members of the AUA met with members of Congress as part of an Alliance “fly-in” to advocate on key federal issues, including the need to retain and strengthen MIPS.

The AUA delegation met with 18 Senate and 35 House of Representatives offices and represented urologists from Arizona, California, Louisiana, Maryland, Minnesota, New York, North Carolina, Pennsylvania, and Tennessee. In addition to stressing the need for maintaining a viable fee-for-service option for MIPS, they also expressed support for the Local Coverage Determination Clarification Act, Prior Authorization/Step Therapy reform, the U.S. Preventive Services Task Force Transparency and Accountability Act, the Resident Physician Shortage Education Act, and medical liability reform.

“No other clinician, provider, or health care professional can replace the value offered by specialty physicians,” Dr. Parekh told subcommittee members during the hearing. “To that end, MIPS must be implemented successfully and set up for long-term viability since it will be the only option for many of these specialists to engage in pay-for-performance given they will have no other option than to remain in fee-for-service.”

MIPS is one of two reimbursement tracks established by Congress under the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA). In the second track, physicians can participate in Advanced Alternative Payment Models (APMs) and potentially earn incentives and increased reimbursement. Although some specialty organizations, including LUGPA, are working to establish APMs for specific services, reimbursement for most services by most urologists will fall under MIPS.

Dr. Parekh noted that several Alliance member organizations working on developing APMs have been told by officials at the Center for Medicare & Medicaid Innovation that models centered on primary care were the agency’s priority.

“It is frustrating to be viewed as a costly part of the Medicare program,” said Dr. Parekh.

“The MIPS program provides the only mechanism for many specialists and subspecialists to engage in federally-sponsored quality improvement and demonstrate their commitment to deliver high-value care.”  

PARAG PAREKH, MD  
ALLIANCE OF SPECIALTY MEDICINE

“while simultaneously being turned away when we present proactive, innovative solutions and proposals.”

Despite that frustration, Dr. Parekh said MIPS allows specialists without suitable Advanced APM opportunities “a fair opportunity to remain in fee-for-service while continuing to measure, report, and improve performance on key areas of clinical quality improvement initiatives, and more importantly, continue to deliver high-quality care to America’s senior and disabled population.”

Starting in 2019, the quality incentive programs that existed prior to MACRA, including the Physician Quality Reporting System, Meaningful Use, and the Value-based Payment Modifier, will be combined and streamlined into a single new value-based payment system.

Utilizing tools like EHR technology and qualified clinical data registries, eligible professionals will transition to MIPS as the sole quality reporting system. As part of this adjustment, the penalties associated with the old incentive programs expired. Under MIPS, eligible professionals’ reimbursement will be adjusted based on four categories: Quality, Cost, Advancing Care Information, and Improvement Activities.

Each eligible clinician reporting to MIPS will be given a composite score based on performance in these categories, based on a scale of 0-100. Each year, the Department of Health and Human Services will establish a performance threshold in the form of a mean or median composite score. The score for 2018 was set at 13, rising to 30 for 2019 under the Centers for Medicare & Medicaid Services’ proposed rule for revisions to the Medicare Physician Fee Schedule for calendar year 2019.

Alliance supports MIPS corrections

Dr. Parekh said in his testimony to the subcommittee the Alliance supports technical corrections approved by Congress for the MIPS program in the Bipartisan Budget Act of 2018. They include:

• providing CMS 3 additional years of flexibility to determine the appropriate weight of the MIPS cost category based on the availability of relevant measures.
• provisions allowing CMS to more gradually increase the MIPS performance threshold year-over-year to give physicians the opportunity to implement necessary practice changes as they gain experience and to be certain that practices with fewer resources are not negatively impacted
• elimination of Medicare Part B drugs and other items and services outside the physician fee schedule from the MIPS payment adjustments and determination of MIPS eligibility.

Nevertheless, Dr. Parekh said, additional refinements to MIPS are still needed to reduce the administrative burden and costs that must be borne by physicians.

“A more simplistic and applicable approach will ensure not just greater clinician engagement, but more purposeful engagement,” he said, adding that the Alliance supports “practical solutions that would lessen the complexity of MIPS scoring.”

He said the Alliance supports a proposal by CMS to reduce the number of objectives and measures that physicians would report to be meaningful users of certified electronic health record technology, eliminate the “convoluted scoring construct,” and focus exclusively on a clinician’s performance on a more limited set of measures.

The hearing was the committee’s fourth oversight session since passage of MACRA in 2015. Additional hearings will be held as CMS continues to implement the program.
Adequate translation services crucial; here’s why

Failure to provide interpreter incurs legal, regulatory risk

According to U.S. Census data, there are at least 25 million people in the United States over the age of 3 years who are considered to be Limited English Proficient, or LEP. This population increased by over 80% between the years of 1990 and 2013 (bit.ly/LEPpopulation). This simultaneously represents a significant increase in the number of patients presenting for medical care who may not speak or understand English sufficiently.

Cases highlight need for adequate translation

Failure to provide adequate medical interpreter and translation services for patients who are LEP is not only mandated by The Joint Commission and the Affordable Care Act, but it is a clear and present risk for malpractice litigation. A number of cases have been highly publicized in recent years and underscore the importance of using a certified medical interpreter for every patient who needs it.

In 2010, a Spanish-speaking California patient was to undergo a nephrectomy. The patient signed an informed consent that was in English, and was not provided with a copy in Spanish. He did not have access to a Spanish interpreter. The wrong kidney was removed. When the mistake was caught, the diseased kidney was also removed, leaving the patient with no kidneys (bit.ly/translationerror).

In the mid-2000s in Germany, a translation error on the package label of a knee prosthesis required 47 people to undergo repeat knee replacement.

In 2015, a Macedonian patient was able to use her friend, rather than a certified medical interpreter, at a consultation for a vestibular nerve tumor. She left with the impression that the tumor was malignant, which was not correct.

During surgery, the surgeon severed the patient’s facial nerve, resulting in unilateral palsy. Only after that did she learn that her tumor was not malignant to begin with.

Perhaps the most famous, and costly of all, was the $71 million settlement for an 18-year-old male who presented to an emergency room in a coma. The use of the Spanish word “intoxicado,” which means you ingested something that made you ill, was interpreted as “intoxicated” in English. The patient was treated for drug overdose when he really was suffering a brain hemorrhage. He became a quadriplegic (bit.ly/translationcase).

One study analyzing 35 claims across just four states found that one liability insurer paid $2.3 million in damages or settlements, and $2.8 million in legal fees for situations where a provider failed to provide a professional interpreter (bit.ly/interpreterpolicies).

Clinical, legal risks

There is no question that providing high-quality interpreting and translation services comes at a financial cost; a survey by the American Medical Association found that interpreter services might cost $150 or more per visit, an amount that might exceed a physician’s payment for the visit. However, failure to provide these services potentiates clinical and legal risk, as is apparent from the above cases. Regulatory risks loom as well; under the Affordable Care Act a $70,000 fine, per encounter, may be imposed for failing to provide a medical interpreter (bit.ly/propertranslationerror).

Hospital 30-day readmission rates are higher for LEP patients, which may then lead to reduced federal reimbursement (bit.ly/propertranslationerror). Finally, the Office of Civil Rights has stated that when an LEP patient is denied or delayed care due to language barriers, it represents a form of discrimination. The Office of Civil Rights also mandates that any recipient of Medicare or Medicaid provide adequate language assistance to LEP patients (Pediatrics 2003;1116-14).

Translation and interpreter services provided by Certified Medical Interpreters is the gold standard. Studies have shown that the rate of error is far lower when a professional interpreter with more than 100 hours of training is used (bit.ly/propertranslationerror). These individuals are credentialed through one of two boards and are familiar with medical terminology. Just because someone is bilingual does not mean they can be a medical interpreter. In fact, just like physicians, certified interpreters are required to obtain continuing education every year (bit.ly/propertranslationerror).

Additionally, the use of family and friends as interpreters is fraught with risk. A certified medical interpreter has a unique skill set that organizations should seek out and celebrate. High-risk situations such as emergency room visits, surgical procedures, informed consent, and medication reconciliation are all areas where use of a certified medical interpreter can be hugely beneficial to all in the moment, and in the future, should a lawsuit arise.

With the use of a certified medical interpreter, a urologist can be much more confident that a urethra is not confused with a ureter, that the bladder vesicle is not mixed up with the seminal vesicle, or that a nephrectomy is not misinterpreted as a nephrostomy.
The UroLift® System is a minimally invasive approach to treating BPH that lifts or holds the enlarged prostate tissue out of the way so it no longer blocks the urethra. It is indicated to treat men who are 45 years of age or older, including those who have an obstructive median lobe.

To learn more about the UroLift System and how it can help you treat more BPH patients, visit UroLift.com

Most common adverse events reported include hematuria, dysuria, micitiurition urgency, pelvic pain, and urge incontinence. Most symptoms were mild to moderate in severity and resolved within two to four weeks after the procedure.

* Images courtesy of Dr. Euclid deSouza

©2018 NeoTract, Inc. All rights reserved.  MAC00706-02 Rev A
Physician-controlled retrieval is here

Introducing the LithoVue Empower™ Retrieval Deployment Device

The critical task of stone basketing can now be controlled by the surgeon – single-handedly.

Take control of your stone procedures and discover a revolutionary way to streamline basketing from start to finish today.

www.BostonScientific.com/LithoVueEmpower