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Genetic testing's role centers on advanced PCa

PARP inhibitors will drive tests' initial use in castrate-resistant disease

ETIC TESTING PROSTATE CANCER GLANCE

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NCER

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Thulium laser shows several advantages

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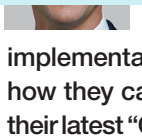
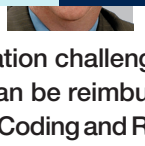
New developments may change treatment of OAB

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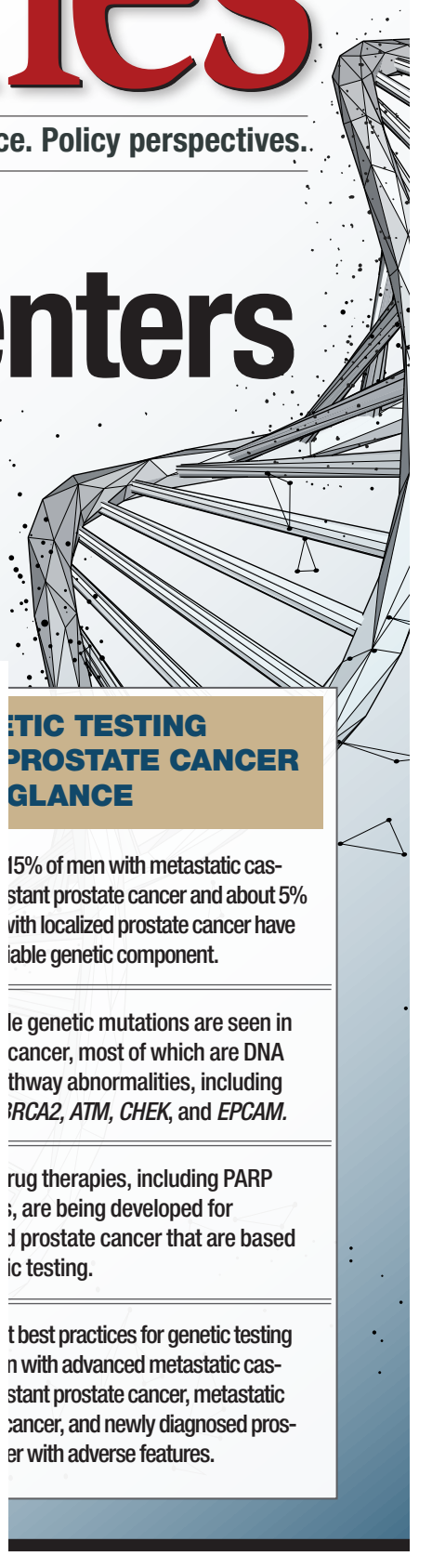

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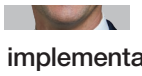

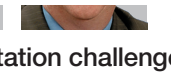

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PARP inhibitors will drive tests' initial use in castrate-resistant disease

Some 15% of men with metastatic castrate-resistant prostate cancer have a clearly identified germline genetic inherited component to their disease, and these patients may soon benefit from new treatment options. In this interview, Leonard G. Gomella, MD, discusses the increasingly important role genetic testing plays in prostate cancer, current obstacles to testing, and when and how it will be carried out.

Dr. Gomella is professor and chair of urology at Thomas Jefferson University and senior director for clinical affairs at the Sidney Kimmel Cancer Center, Philadelphia. He was interviewed by Richard R. Kerr, content channel director of *Urology Times*.

Q: Currently about what percentage of patients with prostate cancer have an identifiable inherited component to their disease?

A: While the majority of prostate cancers are sporadic, approximately 30% of prostate cancers can be identified as being inherited or familial in nature. Prostate cancer is connected genetically to mutated genes that also increase the risk of melanoma, pancreatic, breast, and ovarian cancer not only in the individual but within the family as well.

When you get down to specific clinical situations in prostate cancer, about 15% of patients with metastatic castrate-resistant prostate cancer have an identified germline genetic inherited component. In localized prostate cancer, about 5% of patients have an identifiable genetic component. These numbers in localized disease may not seem big, but these are the patients who are likely to progress to life-threatening prostate cancer and this group is now receiving increased research attention.

There are new therapeutics being developed for advanced prostate cancer that are based on genetic testing. One such example is the poly (ADP-ribose) polymerase (PARP) inhibitors. PARP inhibitors stop the PARP from repairing cancer cells and cause the cells in the presence of a mutated DNA repair gene to die. When the PARP inhibitors get approved for the treatment of advanced prostate cancer they will require a companion diagnostic test that will have to show that the patient with metastatic castrate-resistant prostate cancer has a specific germline mutation to be eligible for treatment.

See **TESTING,** on page 20

GENETIC TESTING FOR PROSTATE CANCER AT A GLANCE

- Some 15% of men with metastatic castrate-resistant prostate cancer and about 5% of those with localized prostate cancer have an identifiable genetic component.
- Multiple genetic mutations are seen in prostate cancer, most of which are DNA repair pathway abnormalities, including *BRCA1, BRCA2, ATM, CHEK,* and *EPCAM.*
- New drug therapies, including PARP inhibitors, are being developed for advanced prostate cancer that are based on genetic testing.
- Current best practices for genetic testing are in men with advanced metastatic castrate-resistant prostate cancer, metastatic prostate cancer, and newly diagnosed prostate cancer with adverse features.

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Coding and Reimbursement

How to code for urologic care during the COVID-19 pandemic

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BLADDER CANCER

Clinical Updates

53% of CIS patients achieve CR with nadofaragene

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For the full article, please turn to page 6

SEE WHAT MORE MAY BE BEHIND THEIR STONE[1]

A kidney stone may be a sign of a metabolic stone disease, such as primary hyperoxaluria type 1 (PH1), that can result in progressive renal impairment.[1-3] So, any unusual presentation among stone formers merits further investigation[1]:

CHILD/ADOLESCENT	ADULT	
• Any stone[1] • Family history of stones[1]	• Recurring stones[1] • Multiple or bilateral stones[1]	• Stones may be larger on average, such as staghorn stones[4-7] • Family history of stones[1] • Biochemical composition (eg, high proportion of calcium oxalate monohydrate, cystine, xanthine, uric acid)[1,8]

In the workup of such patients, a specialist may identify a mutation or biochemical component as the underlying cause of kidney stone formation.[1,9] Once suspected, diagnosing PH1 can be straightforward.[10,11] Prompt management may help to mitigate damage that may result in the need for burdensome supportive care, such as dialysis for some patients.[3,12,13]

BEHIND THE STONE™

Refer your patients for a full metabolic workup when you suspect a metabolic stone disease[1] and visit AboutPH1.com

Alnylam® PHARMACEUTICALS

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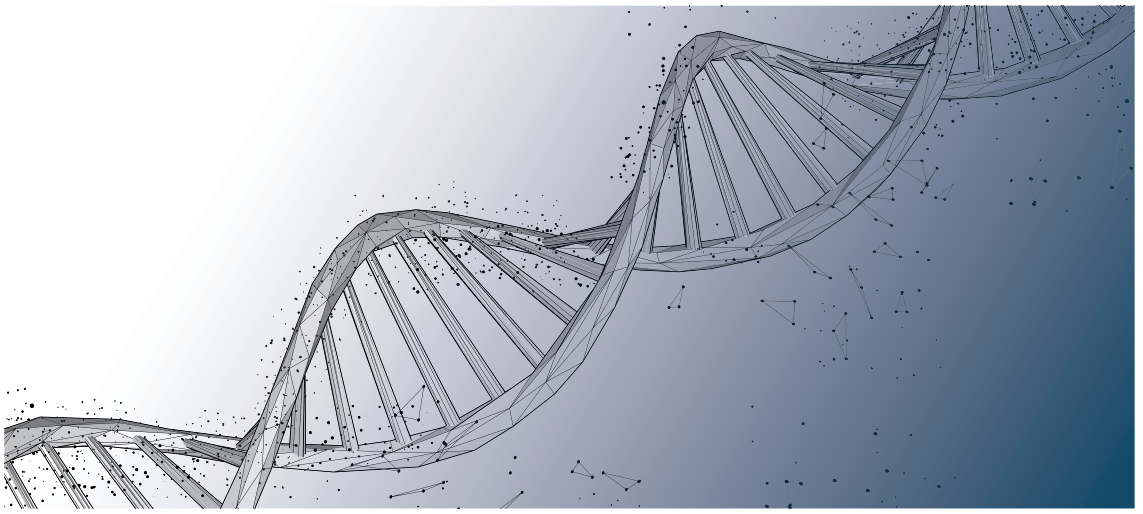

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Chairman's Letter

The pandemic emergency: Is this the new normal?

MIKE HENNESSY, SR

Mike Hennessy, Sr is Chairman and founder of *Urology Times'* parent company, MJH Life Sciences.

The effects of the ongoing coronavirus pandemic permeate every aspect of daily life on a global level. Schools, restaurants, and movie theaters sit silent and empty. Sports seasons have halted dead in their tracks (or have yet to begin). Much of the population remains cloistered in their homes (indeed, this issue of *Urology Times* was produced entirely out of "home" offices).

All of us, regardless of location or profession, have been confronted with the "new normal" of life under a global pandemic. For urologists, myriad challenges have manifested themselves. Does the office remain open? If so, what measures need to be implemented for the safety of patients and staff? Are there elective procedures that can or must be postponed until the crisis abates? What is considered an "elective" procedure? Can virtual visits take the place of office appointments, and if so, how can this be implemented?

To address the latter topic, Adam J. Gadzinski, MD, MS, Chad Ellimoottil, MD, MS, Anobel Y. Odisho, MD, MPH, Kara L. Watts, MD, and John L. Gore, MD, MS, reached out to *Urology Times* with an extremely timely and informative article outlining a "crash course" in teleurology. Given the urgency of the present situation, we felt this warranted publication as a Guest Editorial in this month's issue (page 5).

Our coronavirus resources do not end there. In this issue, Jonathan Rubenstein, MD, and Mark Painter offer a comprehensive primer on reimbursement for telemedicine (page 38). Jeff Witz, CFP, delivers advice on weathering the crisis from a financial standpoint (page 44).

Moreover, we continue to receive incredible contributions from members of our editorial advisory board, which can be found online at *www.urologytimes.com/coronavirus*. Henry Rosevear, MD, has composed thoughtful pieces outlining best practices for physician's offices as well as what might be considered to be elective procedures. Neal D. Shore, MD, contributed a guest blog post on the topic of precision medicine and its role in helping urologists to stratify and prioritize patients. American Board of Urology Executive Director J. Brantley Thrasher, MD, wrote about what the ABU is doing to reduce the recertification burden on urologists and their practice. Gopal H. Badlani, MD, and Bradley A. Erickson, MD, have also composed articles about this unprecedented time.

This month's issue of *Urology Times* maintains our deep array of clinical and practice management content. On the cover, we feature a Q&A interview with Leonard G. Gomella, MD, who provides an update on the rapidly expanding role of genetic testing in patients with prostate cancer. Other highlights include Badar M. Mian, MD's analysis of a recent study evaluating active surveillance protocols in men with Grade Group 1 prostate cancer (page 28) and an installment of "Speak Out" in which urologists weigh in on whether MRI fusion biopsy is the new gold standard for diagnosing prostate cancer (page 30).

Other clinical coverage to watch for includes an interview with BPH expert Kevin T. McVary, MD, regarding the wave of minimally invasive surgical therapies for BPH (page 32), a report suggesting an association between unhealthy diets and semen quality (page 34), and an article discussing recent research evaluating the SuperPulse Thulium Fiber laser for treating stones (page 35). Also be sure to read this month's "Hands On" article Nathan Chertack, MD, Gary Lemack, MD, provide on overview of exciting new developments in the overactive bladder/incontinence space (page 36).

Included with this issue of *Urology Times* is the first issue of the newly redesigned *Urologists in Cancer Care*. With this quarterly publication, we will provide practical and up-to-date information for practicing urologists who manage advanced genitourinary malignancies, with particular focus on prostate, bladder, and kidney cancers. The publication aims to provide reviews and insight on all aspects of cancer diagnosis, treatment, and operationalizing service lines. We feel *Urologists in Cancer Care* will serve as a useful and informative resource for urologists, and we hope you enjoy.

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Teleurology: A crash course during the COVID-19 pandemic

ADAM J. GADZINSKI, MD, MS; CHAD ELLIMOOTTIL, MD, MS; ANOBEL Y. ODISHO, MD, MPH; KARA L. WATTS, MD, AND JOHN L. GORE, MD, MS

Dr. Gadzinski is a senior fellow and acting instructor of urologic oncology, University of Washington, Seattle; **Dr. Ellimoottil** is assistant professor of urology, University of Michigan, Ann Arbor; **Dr. Odisho** is assistant professor of urology, University of California, San Francisco; **Dr. Watts** is assistant professor of urology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY; and **Dr. Gore** is associate professor of surgery (urology), University of Washington, Seattle.
Disclosure: Dr. Odisho had a prior consulting relationship with Vsee from January 2019 to January 2020.

In response to the COVID-19 pandemic, multiple emergency measures have dramatically changed the policies and requirements for telemedicine in the United States. On March 13, 2020, Secretary of Health and Human Services (HHS) Alex Azar authorized waivers and modifications under Section 1135 of the Social Security Act, retroactive to March 1, 2020, to lift telemedicine restrictions. Medicare Part B beneficiaries are now eligible to participate in video visits from any location, including their home, CMS said.

We aim to briefly summarize these changes, provide resources for urologists (from the AUA and CMS), and give practical guidance for quickly launching or scaling a telemedicine program. We primarily focus on video visits, which are live simultaneous audio and visual interactions with patients via a videoconferencing platform. (Also see a table summarizing updated Medicare Part B policy on video at *bit.ly/teleurology.)*

Given that most urologic outpatient visits are non-urgent, almost all in-person visits should be eliminated out of appropriate concern for COVID-19. Continuing urologic care now will mitigate the later surge of patients needing care once this crisis is over. Video visits may also provide some financial stability to urology practices during this time when surgical reimbursements will be greatly reduced. Finally, with uncertainty surrounding the duration of the current State of Emergency and the enacted telemedicine changes beyond this period, investing in telemedicine now will likely benefit urologists in the long term.

Several platforms can be used to perform video visits. Most insurance companies require that the visit has an audio and visual component for real-time communication. A desktop, laptop, smartphone, or tablet can all be used as long as they have a webcam and microphone. The visit should be performed through a reliable and secure platform, which can be integrated into the electronic medical record or be a stand-alone product. Many platforms, such as Skype for Business, Updox, VSee, Zoom for Healthcare, Google G Suite Hangouts Meet, and Doxy.me meet HIPAA compliance requirements.

During the COVID-19 pandemic, the HHS Office for Civil Rights announced that providers can use non-HIPAA-compliant tools to deliver care. Because this federal rule may not impact individual state's laws, providers should prioritize a HIPAA-compliant platform. This will allow for sustainability of new telemedicine programs post-pandemic.

Physicians should follow standard guidelines for documenting and billing video visits, with three key differences. First, the physical exam will be limited. Although established patient billing criteria does not require a physical exam, the absence of a physical exam limits the ability to achieve Level 4 and 5 billing for established and new patients. Therefore, it is generally recommended that time-based billing be used and documented. Second, the claim should include a Place of Service = 02 or a modifier code (GT/95) to indicate the service was performed using telemedicine. While Medicare does not require a modifier code, several private payers require this code. Lastly, provider documentation should include that the visit was conducted via a live face-to-face video conference, the location of the patient (originating site), and the provider's location (distant site).

Insurance reimbursement for video visits varies among payers. Most will reimburse for video visits, but coverage is limited to select locations. Historically, payers required patients to be physically located in a rural medical facility or a designated Healthcare Professional Shortage

See **TELEUROLOGY** page 11

53% of CIS patients achieve complete response with nadofaragene

Nearly half of patients maintain response at 1 year in phase III trial

Nadofaragene firadenovec, a novel intravesical gene-mediated therapy, achieved complete response in 53.4% of patients with bacillus Calmette Guérin-unresponsive carcinoma in situ, according to findings from a phase III trial. The drug is currently under FDA review. First author Stephen A. Boorjian, MD, professor of urology at Mayo Clinic, Rochester, MN, discusses the study results and their implications.

Gina Columbus
Managing Editor, *OncLive*

Q: Please provide a little background on this agent and some of the previous study data we've seen with it.

A: Nadofaragene firadenovec is an interferon-based adenoviral vector. It is administered into the bladder, or intravesically. It's given one time every 3 months. The concept is that the agent allows the bladder cancer cells and the normal bladder cells to produce the protein interferon that acts as an anti-cancer agent. By delivering it into the bladder, it creates a local bioreactor to produce interferon. We previously conducted a phase II trial in which we found that 35% of patients treated with the drug were high grade recurrence free at 12 months. That sort of promising preclinical data plus that phase II trial data led to the development of this phase III trial.

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STEPHEN A. BOORJIAN, MD

Q: What was the design of this current phase III trial?

A: In the phase III trial, we had 157 patients who were ultimately treated with the drug. It was a single-armed trial. The classification of patients who were eligible for the trial were those with BCG-unresponsive, nonmuscle-invasive bladder cancer, so they had high-grade disease. They had been previously treated with BCG—either two induction courses of BCG, one induction course and maintenance BCG, or they had a recurrence of high-grade T1 disease at the first evaluation after single induction course of BCG.

Q: What were the main findings?

A: The primary endpoint of the trial was the complete response rate among patients with carcinoma in situ at any point after their treatment. The efficacy results showed that 53.4% of patients with carcinoma in situ achieved a complete response after treatment. That is the trial's principal finding. The second finding that was of importance was that the responses we saw in this population were largely durable; 45.5% of patients with carcinoma in situ who achieved a complete response maintained that response at 12 months.

Q: Please discuss what the study revealed about the drug's safety.

A: The agent was generally well tolerated. There were three patients in total that stopped treatment because of a treatment-emergent adverse event. The vast majority of adverse events that patients experienced during the study were irritative lower urinary tract symptoms, which is to be expected based on the mode of delivery, the patient population, and the bladder cancer diagnosis.

Q: Are there any quality of life data yet?

A: Not yet. We have the adverse event data in the short term, as we've collected here. We don't have patient-reported outcomes or quality of life data to report at this time. But I think going forward, that's going to be a very important area to look at, along with the durability of responses as the trial data matures.

Q: What future areas of research do you see being explored following the release of these findings?

A: There are a number of exciting opportunities that these data show us. I think one area of future investigation may be using biomarkers to help select patients for treatment. One area of future study may be to look at combination therapies with other available agents in this disease space. Another area of potential future investigation may be to look at using this agent in other nonmuscle-invasive bladder cancer disease states. I think there are a lot of exciting directions that this can be taken. UT

STUDY SHOWS E-CIGARETTE USE, BLADDER CA LINK

Biomarkers of carcinogens, including several with a strong link to bladder cancer, were found to be present in the urine of e-cigarette users, according to a study published in *European Urology Oncology* (March 7, 20 [Epub ahead of print]).

"Although there is no definitive case yet linking bladder cancer to vaping, it may be reasonable to suspect that decades down the road after exposure to these byproducts, people who vape may be at risk of developing bladder cancer," Marc Bjurlin, DO, MSc, of the University of North Carolina Lineberger Comprehensive Cancer Center, said in a press release.

Researchers performed a systematic literature search using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, and included PubMed, Embase, Web of Science, and Cochrane Central Register of Controlled Trials. The initial search identified 1,385 articles, 22 of which met the final inclusion criteria and were included in the analysis.

Overall, the literature described 40 different parent compounds and four metals found in the urine of e-cigarette users. Since each parent compound has the ability to be metabolized several different ways, 63 unique toxicant or carcinogenic metabolite biomarkers were identified.

Compared with nonuser controls, e-cigarette users had higher concentrations of urinary biomarkers of several carcinogenic compounds linked to bladder cancer. However, the majority of studies were limited by heterogenous reporting and a dearth of controls who had never smoked.

"People who have decades of exposure to these carcinogens from vaping map be at risk for developing malignancies, especially bladder cancer," said Dr. Bjurlin.

PARP inhibitor shows no benefit in urothelial Ca trial

One-fourth of patients exhibit stable disease as best response, data indicate

Wayne Kuznar
UT Correspondent

SAN FRANCISCO—The PARP inhibitor rucaparib failed to induce confirmed responses in an open-label phase II trial of patients with recurrent or advanced urothelial carcinoma. As such, the study will not advance, said Petros Grivas, MD, PhD, at the Genitourinary Cancers Symposium in San Francisco.

"Unfortunately, in the ATLAS trial, we did not see any confirmed responses. About a quarter of the patients exhibited stable disease as best response," said Dr. Grivas, clinical director, Genitourinary Cancers Program, University of Washington, Seattle. Subgroups based on homologous recombination deficiency (HRD) did not respond differently from the overall study population.

"The trial was discontinued because preliminary efficacy results did not meet protocol-defined continuance criteria, suggesting that rucaparib monotherapy may not provide a meaningful clinical benefit to unselected patients with metastatic urothelial carcinoma," he said.

A significant proportion of patients with urothelial carcinoma may exhibit HRD based on deleterious alterations in a gene involved in DNA damage response and/or high genome-wide loss of heterozygosity (LOH), which is a marker of genomic scarring and genomic instability.

"Rucaparib has also shown benefit in patients who have tumors that are homologous recombination proficient, which means they do not harbor mutations in DNA damage response genes," Dr. Grivas said.

Rucaparib is approved in the United States and European Union for use as a treatment or maintenance treatment for patients with recurrent ovarian cancer. The investigators hypothesized that a subset of urothelial tumors might be susceptible to PARP inhibition, leading to the design of the phase II ATLAS trial.

Eligibility for ATLAS included patients with metastatic, locally advanced/unresectable urothelial carcinoma with measurable disease, based on RECIST (version 1.1) and confirmed radiographic progression of disease after one to two prior lines of therapy for advanced or metastatic disease. The protocol called for mandatory tissue collection ≤28 days before the first dose of rucaparib or archival tumor collection collected ≤6 months before rucaparib treatment, with no intervening antitumor therapy.

The rucaparib dosage was 600 mg twice daily. Treatment was continued until radiographic disease progression or unacceptable toxicity. Of the 97 patients enrolled, 76 had adequate tissue available for analysis. Most tissue samples (88.2%) had been obtained within 6 months of rucaparib initiation.

The median genomic LOH in ATLAS participants was similar to that found in data from the Cancer Genome Atlas-Urothelial Bladder Carcinoma, Dr. Grivas said. The median tumor mutational burden was 6.3 mutations/Mb, and all tumor samples with known status were microsatellite stable.

The 16-week **clinical benefit rate was 12.6% overall.**

"Unfortunately, in the ATLAS trial, we did not see any confirmed responses. About a quarter of the patients exhibited stable disease as best response."

PETROS GRIVAS, MD, PHD

In the overall study population, the median age was 66 years and 78.4% were men. Fifty-seven patients (58.8%) had received prior cisplatin-based chemotherapy, 34 (35.1%) had prior carboplatin-based chemotherapy, and 771 (3.2%) had prior immune checkpoint inhibitor therapy.

Deleterious alterations in DNA damage repair pathway genes thought to be associated with PARP inhibitor activity, namely *BRCA1*, *BRCA2*, *RAD51C*, and *PALB2*, were relatively infrequent among the patients with sequencing results, at a rate of 9.4% (6 of 64). More than half (52.4%; 33 of 63) of the patient samples exhibited alterations in TP53.

"About a quarter [27 of 95; 28.4%] of the patients exhibited stable disease as best response," Dr. Grivas said. "There were six unconfirmed partial responses, and several patients had a reduction in tumor size. There was no enrichment of the modest activity across different HRD subgroups (positive, negative, or indeterminate)" using a ≥10% genomic LOH cutoff.

The 16-week clinical benefit rate, defined as the proportion of patients with complete response, partial response, or stable disease lasting ≥16 weeks, was 12.6% overall, 15.8% in the HRD-positive subgroup, 6.9% in the HRD-negative subgroup, and 12.8% in the HRD-indeterminate subgroup.

Overall PFS of 1.8 months observed

The median progression-free survival was 1.8 months overall and <2 months across the three HRD subgroups (1.4, 1.8, and 1.8 months in the HRD-positive, -negative, and -indeterminate subgroups, respectively).

The most frequent treatment-emergent adverse events of any grade in the safety population were asthenia (57.7%), nausea (42.3%), anemia or a decreased concentration of hemoglobin (36.1%), and decreased appetite (28.9%). The most frequent grade ≥3 treatment-emergent adverse events were anemia/decreased hemoglobin (20.6%), malignant neoplasm progression (19.6%), and thrombocytopenia/decreased platelet count (11.3%).

Dr. Grivas is a consultant/adviser for AstraZeneca, Bayer, Bristol-Myers Squibb, Clovis Oncology, Driver, Inc., EMD Serono, Exelixis, Foundation Medicine, Genzyme, GlaxoSmithKline, HERON, Janssen, Merck, Mirati Therapeutics, Pfizer, QED Therapeutics, Roche, and Seattle Genetics. For full disclosures, see *bit.ly/atlasdisclosures*. UT

BLADDER CA TEST AVAILABLE FOR IN-HOME SAMPLING

Pacific Edge Diagnostics has introduced a Patient In-Home Sampling Program for its Cxbladder tests that allows patients to self-sample during the coronavirus (COVID-19) pandemic.

"We are committed to helping you and your patients who may benefit from the valuable information that our Cxbladder tests offer. To that end, we have developed a Patient In-Home Sampling Program that will allow your patients to self-sample without the need for them to leave their home," Pacific Edge Diagnostics USA CEO Jackie Walker said. Walker said the company can also ensure timely delivery of results in conjunction with telemedicine patient visits.

Neoadjuvant durvalumab feasible in muscle-invasive bladder Ca

No treatment-related adverse events lead to discontinuation in early trial

Wayne Kuznar
UT Correspondent

SAN FRANCISCO—Durvalumab (IMFINZI) appears to be feasible as neoadjuvant therapy with preliminary evidence of antitumor activity in patients with muscle-invasive bladder who are ineligible for cisplatin-based chemotherapy.

From cohort 1 of a single-center sequential multicohort trial, all 10 patients who entered completed all three doses of durvalumab per protocol and proceeded to radical cystectomy, with only one patient experiencing a grade 3 treatment-related adverse event ([TRAE] anemia), reported Guru P. Sonpavde, MD, and colleagues at the Genitourinary Cancers Symposium in San Francisco.

Eight of the 10 patients had at least 12 weeks of follow-up at the most recent analysis in October 2019. Of the eight, two (25%) had a pathologic response, defined as less than pT2N0 disease, and one (12.5%) had a pathologic complete response (pCR), defined as pT0 disease.

There is no established neoadjuvant therapy for patients with muscle-invasive bladder cancer who are ineligible for cisplatin-based chemotherapy preceding radical cystectomy. Prospective data with PD-1/PD-L1 inhibitors, including pembrolizumab (Keytruda) and atezolizumab (Tecentriq), are encouraging, indicating safety and activity in this setting, said Dr. Sonpavde, director of the Bladder Cancer Program, Dana-Farber Cancer Institute, Boston.

Durvalumab is a PD-L1 inhibitor approved for the treatment of patients with locally advanced or metastatic urothelial carcinoma following platinum-based chemotherapy, but its performance in the neoadjuvant setting had not been tested previously.

"The goal in this phase I trial was primarily to demonstrate feasibility and safety of using durvalumab before radical cystectomy for muscle-invasive bladder cancer. Achieving pCR was a secondary endpoint, which needs to be evaluated in a larger trial employing and powering the trial for pCR as the primary endpoint," Dr. Sonpavde told *Urology Times*.

The data presented here were from cohort 1 of the study, which assessed durvalumab at a dosage of 750 mg intravenously (IV) every 2 weeks for three cycles followed by radical cystectomy 2 to 4 weeks after the last durvalumab dose in patients who were ineligible for or declined chemotherapy.

"Population pharmacokinetic modeling of durvalumab supports the switch from the 10 mg/kg IV every 2 weeks schedule to a flat-dosing regimen of 750 mg IV every 2 weeks, or a regimen of 1,500 mg every 4 weeks IV," said Dr. Sonpavde.

Cohort 2 is examining durvalumab plus oleclumab, a CD73 antagonist monoclonal antibody that enhances the immune response, in 10 patients with cT2 to T4a N0M0 muscle-invasive bladder cancer.

Patients in cohort 1 were a median age of 67 years, 80% were men, and 100% were Caucasian. Eight had clinical stage T2 disease at baseline, one had stage T3, and one had stage T4. Five were not eligible for cisplatin due to grade >1 hearing loss, three due to creatinine clearance level <60 mL/min, and one due to both grade >1 hearing loss and low creatinine clearance. One patient declined chemotherapy.

No dose-limiting toxicities were observed and no TRAEs led to treatment discontinuation. The most frequent TRAEs of any grade were fatigue (n=3), an increase in lipase (n=2), and dry skin (n=2), all of which were grade 1 or 2. Six of the eight patients (75%) who proceeded to surgery underwent cystoprostatectomy; one underwent cystectomy plus hysterectomy, bilateral salpingo-oophorectomy, and anterior vaginectomy; and one underwent cystectomy plus anterior pelvic exenteration.

"While it is reasonable to hypothesize that pCR with PD1/L1 inhibitors translates into prolonged survival (similar to the neoadjuvant chemotherapy setting), validation is required," Dr. Sonpavde said.

AstraZeneca provided funding for the study. For full disclosures, see *bit.ly/abstract507*. UT

Guest Editorial

TELEUROLOGY

continued from page 5

Area during the video visit. This requirement has been relaxed by many private payers, and coverage from any location (including the patient's home) is common. In 29 states, Medicaid does not require patients to be in a specific location for the visit.

More states are permitting visits from home during the COVID-19 emergency. Medicare has historically been the most restrictive on this requirement. However, during the COVID-19 pandemic, Medicare has eliminated this requirement and allows patients to connect from home.

Most states have specific policies regarding telemedicine use. These include documenting informed consent for telemedicine visits in the visit note, limiting some medication prescriptions (mainly narcotics), and requiring a medical license in the patient's state of residence. The Center for Connected Health Policy *(www.cchpca.org)* lists each state's laws and policies alongside emergency laws during the COVID-19 crisis. Providers should understand their state's policies prior to performing telemedicine visits. Although CMS proclaimed that providers with an active non-restricted medical license can provide interstate care without a license in that state, some states require providers to submit an emergency application prior to practicing telemedicine in their state.

Providers should familiarize themselves with their video conferencing platform. We recommend conducting a mock visit to practice initiating and ending a visit and to test screen sharing to display radiology images or diagrams. Patients will invariably have some technical difficulties, and knowing how to troubleshoot is crucial (eg, helping patients turn on video or unmute their microphone). Providers should conduct the visits from a secure location to ensure privacy. Headphones or earbuds may be needed.

Logistical workflow also requires thoughtful implementation to prevent frustration for patients and providers. We have our office staff contact the patient when scheduling the appointment to ensure that the patient understands how to download needed software and log in for the video visit. There are several tip sheets available online to walk patients through telemedicine setup. Many platforms allow for multiple users to join a visit, which can be used to involve family members or an interpreter.

In some circumstances—the patient may not have the capability to perform a video visit, a scheduled video visit may fail, or a health system may not have invested in video visit infrastructure—a phone call may be used in lieu of a video visit. Due to the imperative to keep non-urgent patients at home during the pandemic, many providers are opting for phone calls. Phone calls can be billed CPT 99441-3 and must include a time attestation. Typically, Medicaid does not reimburse telephone calls, though some states have made emergency exceptions. For Medicare, G2012 is the appropriate code for telephone services 5-10 minutes long; there is no higher level for longer conversations.

The COVID-19 State of Emergency has created an environment where urologists can continue to safely provide care through telemedicine. We hope this article helps urologists successfully implement telemedicine and video visits. This will maintain safety both for our patients and the health care workers in our offices. UT

Use of prostate Ca imaging modality leads to management changes

Intended management changes occur in 68% of patients undergoing ^{68}Ga-PSMA-11 PET imaging

Brittany Cote
UT Correspondent

The identification of disease via ^{68}Ga-PSMA-11 positron emission tomography imaging led to management changes in patients with biochemically recurrent prostate cancer, according to results of a prospective, multicenter trial.

In the study, investigators sought to determine the impact of ^{68}Ga-PSMA-11 PET/computed tomography on management of biochemically recurrent prostate cancer. Intended management changes occurred in 68% of patients and were implemented in 78% of patients; the intended change was considered major in 46% of patients.

Results also showed that management pathway aligned with ^{68}Ga-PSMA-11 PET/CT findings and toward systemic therapy or combination approaches for metastatic disease at 44% and 69%, respectively. Moreover, the perceived site of disease was unknown in 68% of patients pre-PET and in 29% of patients post-imaging. Additionally, 150 intended diagnostic tests were prevented by ^{68}Ga-PSMA-11 PET imaging, such as CT (29%) and bone Scans/NaF-PET (35%).

In an interview with *Urology Times* sister brand *OncLive*, lead author **Wolfgang Fendler, MD,** of the department of molecular and medical pharmacology, David Geffen School of Medicine at University of California, Los Angeles, highlighted the potential impact ^{68}Ga-PSMA-11 PET imaging may have on the treatment of patients with biochemically recurrent prostate cancer.

Q: Could you provide some background on this trial?

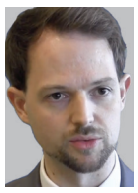
A: ^{68}Ga-PSMA-11 PET is an imaging modality. It is a whole-body scan for patients with prostate cancer and is very easy to be performed. Patients received an intravenous injection of a radionuclide before they were imaged. Afterwards, they had a whole-body imaging done for about 20 to 30 minutes. The image shows us where the prostate cancer is located in the body and can be used as an imaging or staging modality at initial diagnosis, or by clinical recurrence, in patients. The imaging locates the cancer for the physician to make further decisions.

Q: What is it about this imaging modality that has made the community so excited?

A: There was a huge clinical need [for this type of imaging]. Blood tests show that the patient's prostate-specific antigen is rising and then the cancer recurs. The disease is usually located in the pelvis; however, it is not possible to locate [the exact location of] this cancer.

^{68}Ga-PSMA-11 PET is the first modality among other novel imaging tests and is one of the most sophisticated imaging tests. That is why it is being approached as a very promising imaging test.

"There are several entities actively working on FDA approval of ^{68}Ga-PSMA-11 PET. I would expect [it to be approved] within 1 year."



WOLFGANG FENDLER, MD

Q: What were the results that were presented at the Genitourinary Cancers Symposium?

A: We have shown before that the ^{68}Ga-PSMA-11 PET imaging test shows prostate cancer lesions in patients with a rising tumor marker level in about 75% of patients and is very accurate. Now, we went one step further and assessed in a larger patient population [to see] whether or not this imaging test can impact management decisions.

We have assessed 382 patients on whether or not the intended management before the imaging test was done changed after seeing the results of the imaging test. This was assessed using questionnaires that were sent to the referring physicians. They were asked the following questions]: "What is your intended management before doing the imaging test? What is your intended management [after receiving the report]?" and a few months later, "Did you follow this management?"

Using questionnaires, we could show that the imaging test results and the change in the clinical management was found in two-thirds of patients and about half of all patients, respectively. There was either a new type of treatment being added or the treatment modality was completely changed. The study is going into more detail on what types of changes we see in patients and the types of management that follow what we see in imaging. For example, if it is a local disease, physicians tend to change the management to be more local. If there is no disease, they tend to change it to no treatment at all, and if it is a systemic disease then physicians change to systemic or multimodal treatment.

Q: To what extent did ^{68}Ga-PSMA-11 PET alter management of heavily recurring prostate cancer?

A: The change was in 68% of patients with any change in management after ^{68}Ga-PSMA-11 PET imaging. About [48% of physicians considered an intended change and patients were given] a different type of treatment that was not considered before.

The type of changes we saw were an addition of chemotherapy in a patient who had a disease or lesion that was outside of the usual operating field. Typical changes also included an addition of radiation therapy in patients who had lymph nodes detected in the pelvis, with localized disease often undergoing additional radiation therapy to be more effective.

Q: How close are we to FDA approval of ^{68}Ga-PSMA-11 PET? What are the next steps?

A: There are several entities actively working on FDA approval of ^{68}Ga-PSMA-11 PET. I would expect [it to be approved] within 1 year.

If the test is approved, this means it is also becoming available and will be used more often. Before decisions are being made, most patients will undergo additional imaging for the physician and the patient to be informed about further management.

Q: What is the rationale for this type of modality and how it is going to meet the unmet need?

A: This imaging test adds the location [of the tumor] and gives other information that is relevant in the clinical setting. The reason for this is that a lot of the available treatments need the location of the tumor. For example, we need to know which part of the body to apply radiation. The same goes for surgery; we need to know the [exact location] of the tumor. This is a specific need that the imaging test can fill to help physicians and patients to improve future regimens.

Q: Is there anything else about your research that you would like clinicians to know about?

A: Our research was focused on the change in management after this imaging test. It is very important as the next step to show a positive impact on what happens to the patient afterward, as well as the outcome and time until a patient shows another recurrence of the disease. There are several ongoing trials assessing this imaging test in a randomized fashion in comparison with the standard, which is looking at the benefit for the patient. UT

Erleada® (apalutamide) 60 mg tablets

Start early with ERLEADA®

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

In the TITAN study† in patients with metastatic castration-sensitive prostate cancer (mCSPC):

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

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

INDICATION

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

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

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

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

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

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

Embryo-Fetal Toxicity—The safety and efficacy of ERLEADA® have not been established in females. Based on its mechanism of action, ERLEADA® can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA® *[see Use in Specific Populations (8.1, 8.3)]*.

ADVERSE REACTIONS

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

Laboratory Abnormalities—All Grades (Grade 3-4)

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

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

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

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

DRUG INTERACTIONS

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

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

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

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

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

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

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

References: 1. ERLEADA® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for metastatic castration-sensitive prostate cancer. *N Engl J Med.* 2019;381(1):13-24. doi: 10.1056/NEJMoa1903307.

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Brief Summary of Prescribing Information for ERLEADA® (apalutamide)

ERLEADA® (apalutamide) tablets, for oral use

See package insert for Full Prescribing Information

INDICATIONS AND USAGE

ERLEADA is indicated for the treatment of patients with

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Ischemic Cardiovascular Events

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

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

Fractures

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

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

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

Falls

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

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

Seizure

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

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

Embryo-Fetal Toxicity

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

ADVERSE REACTIONS

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

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

Clinical Trial Experience

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

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

Metastatic Castration-sensitive Prostate Cancer (mCSPC)

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

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

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

Table 1: Adverse Reactions in TITAN (mCSPC)

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

[1] Includes fatigue and asthenia
[2] Includes rash, rash maculo-papular, rash generalized, urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash papular, skin exfoliation, genital rash, rash erythematous, stomatitis, drug eruption, mouth ulceration, rash pustular, blister, papule, pemphigoid, skin erosion, dermatitis, and rash vesicular
[3] Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3

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

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

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

[1] Does not reflect fasting values

Non-metastatic Castration-resistant Prostate Cancer (nmCRPC)

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

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

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

Table 3: Adverse Reactions in SPARTAN (nmCRPC)

	ERLEADA N=803		Placebo N=398	
System/Organ Class Adverse reaction	**All Grades %**	**Grade 3-4 %**	**All Grades %**	**Grade 3-4 %**
General disorders and administration site conditions				
Fatigue[1,4]	39	1	28	0.3
Musculoskeletal and connective tissue disorders				
Arthralgia[4]	16	0	8	0
Skin and subcutaneous tissue disorders				
Rash[2]	25	5	6	0.3
Metabolism and nutrition disorders				
Decreased appetite[5]	12	0.1	9	0
Peripheral edema[6]	11	0	9	0
Injury, poisoning and procedural complications				
Fall[4]	16	2	9	0.8
Fracture[3]	12	3	7	0.8
Investigations				
Weight decreased[4]	16	1	6	0.3
Vascular disorders				
Hypertension	25	14	20	12
Hot flush	14	0	9	0
Gastrointestinal disorders				
Diarrhea	20	1	15	0.5
Nausea	18	0	16	0

[1] Includes fatigue and asthenia
[2] Includes rash, rash maculo-papular, rash generalized, urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash papular, skin exfoliation, genital rash, rash erythematous, stomatitis, drug eruption, mouth ulceration, rash pustular, blister, papule, pemphigoid, skin erosion, dermatitis, and rash vesicular
[3] Includes rib fracture, lumbar vertebral fracture, spinal compression fracture, spinal fracture, foot fracture, hip fracture, humerus fracture, thoracic vertebral fracture, upper limb fracture, fractured sacrum, hand fracture, pubis fracture, acetabulum fracture, ankle fracture, compression fracture, costal cartilage fracture, facial bones fracture, lower limb fracture, osteoporotic fracture, wrist fracture, avulsion fracture, fibula fracture, fractured coccyx, pelvic fracture, radius fracture, sternal fracture, stress fracture, traumatic fracture, cervical vertebral fracture, femoral neck fracture, and tibia fracture
[4] Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3
[5] Includes appetite disorder, decreased appetite, early satiety, and hypophagia
[6] Includes peripheral edema, generalized edema, edema, edema genital, penile edema, peripheral swelling, scrotal edema, lymphedema, swelling, and localized edema

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

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

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

[1] Does not reflect fasting values

Rash

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

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

Hypothyroidism

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

DRUG INTERACTIONS

Effect of Other Drugs on ERLEADA

Strong CYP2C8 or CYP3A4 Inhibitors

Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties (sum of unbound apalutamide plus the potency-adjusted unbound N-desmethyl-apalutamide). No initial dose adjustment is necessary however, reduce the ERLEADA dose based on tolerability *[see Dosage and Administration (2.2) in full Prescribing Information]*. Mild or moderate inhibitors of CYP2C8 or CYP3A4 are not expected to affect the exposure of apalutamide.

Effect of ERLEADA on Other Drugs

CYP3A4, CYP2C9, CYP2C19 and UGT Substrates

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

P-gp, BCRP or OATP1B1 Substrates

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

Contraception

Males

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

Infertility

Males

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

Pediatric Use

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

Geriatric Use

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

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

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

OVERDOSAGE

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

PATIENT COUNSELING INFORMATION

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

Ischemic Cardiovascular Events

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

Falls and Fractures

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

Seizures

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

Rash

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

Dosage and Administration

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

Embryo-Fetal Toxicity

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

Infertility

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

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Moderate activity seen with adding pembro to enza for mCRPC

Combination will continue to be evaluated in phase III trial, researcher reports

Caroline Seymour
UT Correspondent

The addition of pembrolizumab (Keytruda) to enzalutamide (Xtandi) showed moderate but durable activity in patients with metastatic castration-resistant prostate cancer (mCRPC) who progressed on enzalutamide, according to findings from cohorts 4 and 5 of the phase II KEYNOTE-199 trial, said lead study author Julie N. Graff, MD.

In the study, patients with chemotherapy-naïve mCRPC who were resistant to enzalutamide were randomized into 1 of 5 cohorts. In cohorts 4 and 5, patients had measurable disease (n=81), or nonmeasurable/bone-predominant disease (n=45), respectively. The majority of patients in both cohorts had PD-L1–negative disease.

In cohort 4, the objective response rate (ORR) was 12%, the disease control rate (DCR) was 51%, and the median duration of response was 6.3 months. In cohort 5, the DCR was 51%. The radiographic progression-free survival was 4.2 months and 4.4 months in cohorts 4 and 5, respectively. Overall survival (OS) was not reached in cohort 4 versus 18.8 months in cohort 5.

The combination had a manageable safety profile. The most common all-grade treatment-related adverse events were fatigue (24%), hypothyroidism (16%), and rash (15%), the latter of which was well managed with steroids.

In an interview with *Urology Times* sister brand *OncLive*, Dr. Graff, associate professor of medicine, Oregon Health & Science University Knight Cancer Institute, Portland discussed the results of the trial, the importance of combination strategies in mCRPC, and the next phase of research for the combination.

Q: Could you provide background on the KEYNOTE-199 trial?

A: KEYNOTE-199 is a multicohort, phase II study that [is sponsored by] Merck. Cohorts 1, 2, and 3 included men with mCRPC who received single-agent pembrolizumab after chemotherapy and next-generation androgen receptor inhibitors. I presented the data from cohorts 4 and 5, which included men with chemotherapy-naïve mCRPC who were progressing on enzalutamide. Cohort 4 included men with measurable disease, and cohort 5 included men without measurable disease, with mostly bone-predominant disease. Patients continued on enzalutamide and received pembrolizumab every 3 weeks until intolerance or disease progression.

Q: How are patients with progressive mCRPC traditionally treated?

A: Currently, the standard of care for patients who progress on enzalutamide varies from place to place. Typically, especially for the men on this trial, we would administer chemotherapy; that might be the next step for many patients. Some providers would consider giving abiraterone acetate (Zytiga) after enzalutamide. Although some responses [can be induced with that approach, we don't see] as many as when it's given up front.

Q: What did you find in cohorts 4 and 5?

A: The primary endpoint of the study was ORR per RECIST v1.1 criteria, which we evaluated in cohort 4. Additional endpoints included DCR, OS, safety, and prostate-specific antigen (PSA) response. We found that 12% of patients in cohort 4 had a confirmed RECIST response, defined as a greater than 30% reduction in tumor size. Far more patients had any level of tumor reduction. However, some patients did not have confirmatory scans. In cohorts 4 and 5, the DCR was 51%. The PSA response rate was about 14% overall. We did see patients with a PSA of close to 0 on this study. We also saw durable responses.

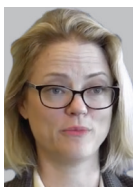
Q: How was the regimen tolerated?

A: There are risks with all of these checkpoint inhibitors. Now that these agents are approved for use in so many disease states, we continue to learn more about them. The combination of enzalutamide and pembrolizumab, or any PD-1 inhibitor, appears to lead to more rashes [for patients]; that was something we were very interested in. We saw that 25% of patients had a rash. Of those patients, only one was grade 3 and required intravenous steroids. The other patients were managed with topical or oral steroids. Otherwise, the safety profile was sort of as expected.

Q: What are the next steps for this research?

A: The next step in this research is to see whether the combination extends survival over the currently available treatment options. Merck has started the KEYNOTE-641 trial, which is trying to answer this question. In that study, which is being done worldwide, patients who have not received enzalutamide or any drug like it will receive enzalutamide [and either pembrolizumab or placebo].

"In general, single-agent checkpoint inhibitors have not been very exciting. We've seen higher responses when they're combined with other drugs."



JULIE N. GRAFF, MD

Q: Should immunotherapy only be evaluated in combination in this space?

A: In general, single-agent checkpoint inhibitors have not been very exciting. We've seen higher responses when they're combined with other drugs. There have been studies with the combination of pembrolizumab plus olaparib (Lynparza), which is a PARP inhibitor, and with chemotherapy, [and it is] kind of surprising that it would work. Combinations are the future. Efforts are underway to combine different types of immunotherapies. For example, studies are evaluating PD-1 inhibitors, such as pembrolizumab, with CLTA-4 inhibitors, such as ipilimumab (Yervoy). UT

Disclosure: Merck Sharp & Dohme Corp. provided funding for the study.

PROSTATE IMAGING, Bx OFTEN MISS CONTRALATERAL TUMORS

Recent research shows contemporary imaging and biopsy techniques often fail to identify contralateral tumors in men presumed to have unilateral prostate cancer—and the results have significant implications for identifying candidates for hemiablation.

A study by researchers at UCLA Health David Geffen School of Medicine found a substantial percentage of patients diagnosed with unilateral prostate cancer based on contemporary imaging and biopsy techniques harbor undetected, clinically significant contralateral disease.

For more about this study, go to *bit.ly/contralateraltumors.*

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Hydrogel spacer lowers rectal bleeding vs. balloon immobilization treatment

Spacer also associated with significantly lower decrease in patient-reported bowel QoL

Cheryl Guttman Krader
UT Contributing Editor

Results from 2 years of follow-up in men undergoing proton beam therapy (PBT) for localized prostate cancer suggest that treatment with the rectal hydrogel spacer (SpaceOAR) provides better rectal sparing than rectal balloon immobilization.

The recently published findings showed that compared with rectal balloon immobilization, treatment with the hydrogel spacer significantly reduced the risk of clinically relevant (grade 2+), late rectal bleeding and was associated with a significantly lower decrease in patient-reported bowel quality of life *(Int J Radiat Oncol Biol Phys* Feb. 6, 2020 [Epub ahead of print]).

Co-author William J. Ellis, MD, told *Urology Times*, "Phase III study results showed that the hydrogel rectal spacer decreased the incidence of late rectal toxicity in men who underwent intensity-modulated radiation therapy for localized prostate cancer. Utilization of PBT is expected to grow, and this study investigated outcomes after PBT with the hydrogel spacer in a real-world setting using data that were prospectively collected over a relatively long follow-up.

"Urologists who do prostate ultrasound and are accustomed to placing fiducial markers for radiation oncologists can easily acquire the skill needed to place the hydrogel spacer."

WILLIAM J. ELLIS, MD

"Treatments often do not perform as well in clinical practice as they do in clinical trials, and yet we found that the rectal-sparing benefit of the hydrogel spacer, particularly for reducing late rectal bleeding, was even greater than expected. These findings can hold interest for urologists who counsel patients about their treatment options for localized prostate cancer," added Dr. Ellis, professor and vice-chair of urology, University of Washington, Seattle.

The single-institution study included data from 267 patients treated for localized, clinical stage T1-4 prostate cancer using conventionally fractionated, dose-escalated PBT from 2013 to 2018. A total of 192 men were treated with rectal balloon immobilization, and 75 men underwent placement of the rectal hydrogel spacer. Dr. Ellis and George R. Schade, MD, assistant professor of urology, University of Washington, placed all of the hydrogel spacers. Rectal balloons were inserted by radiation oncology technicians.

TABLE HYDROGEL SPACER VS. BALLOON: RECTAL BLEEDING RATES

	Hydrogel spacer group	Rectal balloon immobilization group
2-year actuarial rate of any rectal bleeding	13%	35%
2-year actuarial rate of grade 2+ late rectal bleeding	3%	19%

Source: William J. Ellis, MD

The incidence of late rectal bleeding and bowel quality of life were analyzed as co-primary endpoints. Grading of rectal bleeding was done retrospectively using the Common Terminology Criteria for Adverse Events. Bowel quality of life was assessed using the bowel domain of the expanded prostate cancer index composite (EPIC), which was completed at baseline and then every 6 months.

2-year rate of any bleeding higher in balloon group

Median follow-up for patients in the rectal balloon and hydrogel spacer groups was 19 and 22 months, respectively. The 2-year actuarial rate of any rectal bleeding was almost threefold higher in the rectal balloon group compared with the hydrogel spacer group (35% vs. 13%). The 2-year actuarial rate of grade 2+ late rectal bleeding was only 3% in those in the hydrogel spacer group versus 19% among men who had rectal balloon immobilization (p=.003). No men in the hydrogel spacer group had a grade 3 bleeding event compared with two men in the rectal balloon cohort. No patients had a grade 4+ bleeding event.

"The cumulative incidence of grade 2+ rectal bleeding among men treated with the hydrogel spacer remained relatively low and stable throughout follow-up, whereas it rose fairly steadily between 6 and 24 months in the rectal balloon cohort," Dr. Ellis observed.

Additional analyses were done to identify variables predictive of grade 2+ rectal bleeding. In univariable analysis, a significant correlation was found only with rectal dose. In multivariable analysis, receipt of the hydrogel spacer was identified as protective. Compared with the rectal balloon immobilization group, men who had the spacer hydrogel had an 85% lower risk for having grade 2+ rectal bleeding (p=.01). The only other independent predictor of grade 2+ rectal bleeding was anticoagulation use, which increased the risk by fivefold.

The quality-of-life analysis showed that the mean EPIC-bowel domain score was similar in the patients in the rectal hydrogel spacer and rectal balloon groups at baseline (92.3 vs. 93.4). Although it was decreased from baseline in both groups at all follow-up intervals, the decrement was consistently less in the hydrogel spacer group, and the separation between groups favoring the hydrogel spacer cohort increased with lengthening follow-up.

"At 2 years, there was a 5.5-point absolute difference in the EPIC-bowel score favoring the hydrogel spacer group. The difference was statistically significant (p=.030) but also can be considered clinically significant as a minimum difference of five points has been suggested to be clinically meaningful," Dr. Ellis said.

The study was also designed to compare dosimetric parameters for PBT in the two rectal sparing procedure groups. Analysis of those data showed that the rectal hydrogel spacer was associated with significantly improved rectal dosimetry while maintaining excellent target coverage.

Dr. Ellis noted that although some radiation oncologists place the rectal hydrogel spacer themselves, the procedure is done by urologists at the University of Washington.

"Urologists who do prostate ultrasound and are accustomed to placing fiducial markers for radiation oncologists can easily acquire the skill needed to place the hydrogel spacer," Dr. Ellis said. "The radiation oncologists at our institution appreciate our assistance, and it has led to a mutually satisfying collaborative relationship." UT

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mCRPC = metastatic castration-resistant prostate cancer.
†Androgen receptor (AR)-targeted therapies include Erleada™ (apalutamide), Zytiga® (abiraterone), and Xtandi® (enzalutamide).

TESTING

continued from page 1

Q: What have been the major developments in prostate cancer genomics and germline testing in particular over the last year or two?

A: What we're seeing is that patients with advanced and aggressive prostate cancer are increasingly undergoing germline genetic testing for inherited prostate cancer risk, not only in the individual but also in their family members. Testing other family members for an inherited cancer risk is known as "cascade testing." More medical organizations are advocating that men who have *BRCA1*, *BRCA2*, and related abnormalities should be aggressively screened for prostate cancer. This is a big take-home message over the last few years.

Our colleagues in Europe, particularly in England, who have done extensive population studies, are promoting this. They've shown that if a man has one of these inherited abnormalities in the DNA repair pathway—*BRCA1* and *BRCA2* are the highlights right now but there are others—he should undergo more focused screening for prostate cancer than a man who does not have such abnormalities.

Today, how does a man without a diagnosis of prostate cancer come to be identified with one of these mutated genes? Most likely he has a relative who has had aggressive prostate cancer and has undergone genetic testing or he's had a female first-degree relative—mother or sister—who had hereditary breast or ovarian cancer, and it's been recommended based on a family pedigree that he undergo germline genetic testing.

Q: The second International Prostate Cancer Consensus Conference was held in Philadelphia in October 2019. The meeting emphasized implementation of genetic testing for inherited prostate cancer. What have been the major developments in how genetic testing is implemented?

A: The second International Prostate Cancer Consensus Conference focused on the practical aspects of testing for these genetic alterations in men with prostate cancer. The consensus sought to optimize testing strategies integrating evolving genetic data and growth of panel options, recommend consistency in testing indications and genetically based management, and identify alternate evaluation models addressing a shortage of genetic services.

How should men with prostate cancer be evaluated for the need to undergo genetic testing? Ideally, a provider identifies a patient as having a potential genetically inherited mutation that predisposes to prostate cancer or the patient has an advanced or aggressive cancer. A prostate cancer genetic panel can be ordered, or the patient can be referred to a genetic counselor.

The fact is that we have a nationwide shortage of genetic counselors.

The reality is that not all men with prostate cancer need to undergo genetic testing. In the ideal setting, a genetic counselor would go over the characteristics of the individual's tumor, the family pedigree, and what other cancers may be in the family and come up with a reasonable approach to testing. There would be a recommendation for the individual to undergo genetic testing or for genetic testing in family members.

How should we handle genetic testing when there is currently limited access to genetic counselors in the United States who have expertise in prostate cancer? The fact is that we have a nationwide shortage of genetic counselors. What alternative evaluation models are needed was a central theme of our second consensus conference. Many genetic testing reference labs have helped to deal with this limitation by providing basic initial genetic consultation by phone.

Q: What are some of the current best practices in the use of these tests?

A: Right now, the best practices are genetic testing in men with advanced metastatic castrate-resistant prostate cancer, metastatic prostate cancer, and newly diagnosed prostate cancer with adverse features. Organizations supporting genetic testing for this group of high-risk men include the National Comprehensive Cancer Network (NCCN). As noted, the PARP inhibitors, which are already available and FDA approved for ovarian and breast cancer, are a significant driver of this. We're now looking for PARP inhibitors to be approved, probably sometime in the first half of 2020, for metastatic castrate-resistant prostate cancer.

The PARP inhibitors are found to be most effective in cases where the patient has an inherited mutated gene in the *BRCA1/BRCA2* and other DNA repair pathway. The approval for the PARP inhibitors will include pharmacogenomic testing to e determine eligibility for these drugs. From a best practice standpoint, using genetic testing in men with advanced castrate-resistant prostate cancer is a good approach because it will give men with difficult-to-manage prostate cancer more options, including participation in clinical trials.

Q: Does genomic testing have a role beyond metastatic disease?

A: We're really just beginning to explore that. If a patient has high-risk prostate cancer—a very high Gleason score, high PSA, advanced clinical stage, adverse features, or intraductal carcinoma—while his cancer might not yet be metastatic or castrate resistant, NCCN guidelines indicate he should undergo genetic testing. What's happening, as with everything in medicine, is that you start with the most advanced clinical scenarios and then begin to investigate earlier stages of a disease.

I believe one of the most exciting areas for genomic testing is the area of active surveillance. One paper in particular by Dr. Ballentine Carter from Johns Hopkins looked at doing genetic profiling on men who are in active surveillance *(Eur Urol* 2019; 75:743–9). It showed that if you have an altered inherited DNA repair pathway gene like *BRCA1* or *BRCA2*, you are more likely to fall off the active surveillance pathway because of grade progression on subsequent biopsy.

The PARP inhibitors are found to be most effective in cases where the patient has an inherited mutated gene in the *BRCA1/BRCA2* and other DNA repair pathway.

Q: Did the consensus conference address gaps in prostate cancer guidelines?

A: We identified a series of priority genes that should be used to direct precision treatment of prostate cancer such as *BRCA1*, *BRCA2*, *MSH2/MSH6*, *ATM*, and other mismatch repair (MMR) genes. In non-metastatic PCA, consensus testing

TABLE COMMON MUTATED GENES THAT INCREASE PROSTATE CANCER RISK

MUTATED GENE	MECHANISM
ATM	DNA damage repair
BRCA1	DNA damage repair
BRCA2	DNA damage repair
CHEK2	DNA damage repair
EPCAM	Upregulate c-myc
HOXB13	Interacts with the androgen receptor
*MLH1**	DNA repair
*MSH2**	DNA repair
*MSH6**	DNA repair

*Source: *Lynch syndrome genes (also known as hereditary non-polyposis colorectal cancer or HNPCC) that increase the risk for a number of cancers, including prostate cancer*

recommendations emerged encompassing personal, pathologic, and family history criteria. Priority genes for active surveillance discussions primarily focused on *BRCA2* and *ATM*. Our 2019 consensus paper is currently in press in the *Journal of Clinical Oncology*, and we are hopeful that the recommendations of our interdisciplinary group will help address issues in prostate cancer guidelines. The NCCN has been very good at rapidly responding to new developments and updating their recommendations in this area over the last 2 years.

Q: What other issues were discussed at the consensus conference?

A: There was a great deal of discussion about the best way to share the information from genetic testing with the patient and the best way to counsel them. The federal GINA (Genetic Information Nondiscrimination Act of 2008) laws protect individuals from health insurance and employment discrimination who have undergone genetic testing. Providers who are ordering genetic testing should be aware that these laws may not apply to patients who are interested in long-term health care, disability insurance, and related issues.

An area of group discussion centered on whether genetic testing should be done reflexively. Or should you actually have informed consent before the test is ordered? A focus of this discussion was the fact that we have such a significant shortage of genetic counselors in the United States, and we need to look at genetic testing alternatives until we build up an adequate pool of genetic counselors.

Q: How are practicing urologists being educated about genetic testing for prostate cancer?

A: I recommend keeping up with the latest NCCN guidelines. I don't think urologists are as engaged in this area as other medical specialists because genetic testing came into our clinical practices very quickly. The department of urology at the Sidney Kimmel Cancer Center conducted the first international consensus on genetic testing for inherited prostate cancer risk in 2017 because we realized that scientific information was coming at a very rapid rate, but it was not being acted upon in general urology practice. I believe we need to improve training of our residents, in particular, in this area.

Providers who are trained in medical oncology tend to have more background in this area, simply because breast and ovarian cancer are so far ahead of prostate cancer in the genetic testing world. Most fellows who are completing medical oncology training have had some formal genetic counseling and testing experience because of the well-established world of breast cancer genetic testing.

We are very interested in having urologists get up to speed and include genetic testing in our training programs. The Society of Urologic Oncology and the AUA have partnered in educational programs in advanced prostate cancer for residents, fellows, advanced practice providers, and practicing urologists. We have incorporated educational modules that address genetic testing and what are the best practices today. We need to do more to have urologists engaged considering the PARP inhibitors are oral agents that many urologists who treat advanced prostate cancer will begin to prescribe.

We can't just ask those family history questions anymore. We've got to expand our questioning and ask about pancreatic, breast, and ovarian cancer, melanoma, as well as Lynch syndrome and colorectal cancer.

Q: Who should be conducting genetic testing for prostate cancer?

A: Most urologists outside of major medical centers don't have easy access to prostate cancer-trained genetic counselors and can easily order genetic panel testing from a variety of commercial labs. Urologists are used to asking male patients if their father or grandfather or brothers had prostate cancer. We can't just ask those family history questions anymore. We've got to expand our questioning and ask about pancreatic, breast, and ovarian cancer, melanoma, as well as Lynch syndrome and colorectal cancer. The urologist needs to start asking these questions and identify that a patient may have a familial hereditary or potentially inherited form of prostate cancer. (Also see, "Hereditary vs. inherited prostate cancer," below.)

Q: Do we know yet precisely which genetic mutations to look for in prostate cancer, or is that a work in progress?

A: There are a lot of candidate genes; the list includes at least 20 or 30 genes. We have what I would call the "top" mutated genes, most of which are DNA repair pathway abnormalities: *BRCA1*, *BRCA2*, *ATM*, *CHEK*, and *EPCAM*, among others.

We certainly don't have all the genes identified yet. If you look at the commercial prostate cancer panels, most will have a core of those 10 to 12 most common genes, but many of the genetic testing companies test for many more genes than that. Unfortunately, we still don't know how to interpret a lot of those other genes, specifically when it comes to prostate cancer. (See table on page 20 that summarizes some of the most common mutated genes that increase prostate cancer risk.)

Q: Are there genetic tests for prostate cancer that are in development and might become commercially available?

A: There is considerable work being done with single nucleotide polymorphism (SNP or "snip") tests. These tests look not necessarily at identified genes that are mutated but at identified variable DNA sequences—SNPs associated with prostate cancer. Some researchers feel that looking at a few short sequences of DNA as opposed to a whole known gene may be more useful in some patients. Those tests are just becoming available.

Q: Is there anything else you would like to add?

A: This is an area that is exploding in urology, and urologists need to keep abreast of what's happening. We are working on alternatives to identify ways to address a shortage of genetic services. At the Sidney Kimmel Cancer Center, our team members are involved in graduate training programs and are developing an app to help medical oncologists and urologists potentially screen patients for appropriate prostate cancer genetic testing. UT

HEREDITARY VS. INHERITED PROSTATE CANCER

It's important to draw a distinction between hereditary and inherited prostate cancer, according to Leonard G. Gomella, MD.

"Hereditary prostate cancer is a much broader umbrella that suggests there may be genetic alterations that are passed down from generation to generation that may increase the risk of developing an aggressive prostate cancer or other cancers known to cluster in families," Dr. Gomella said. "Inherited prostate cancer, by comparison, involves genes such as the *HOXB13* gene, a gene in family members where multiple younger men develop aggressive prostate cancer. Most of the mutated genes we're talking about in prostate cancer are DNA damage response genes—*BRCA1, BRCA2, ATM*, and others. They can result in increased heredity prostate cancer risk or may simply suggest that there may be something going on in the family that increases the risk of other associated cancers in multiple family members.

"It's also important to point out that these mutated genes do not cause prostate cancer," he pointed out. "This is a common misconception. They don't cause the cancer, but it turns out if you have one or more of these of these mutated genes, it does something to make prostate cancer a more aggressive, more lethal form."

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IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

YONSA® can cause fetal harm and potential loss of pregnancy.

Please see the following pages for Important Safety Information and Brief Summary of the Full Prescribing Information.

IMPORTANT SAFETY INFORMATION, CONTINUED
WARNINGS AND PRECAUTIONS

Hypertension, Hypokalemia, and Fluid Retention Due to Mineralocorticoid Excess: YONSA® may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with YONSA®.

Closely monitor patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, such as those with heart failure, recent myocardial infarction, cardiovascular disease, or ventricular arrhythmia. The safety of YONSA® in patients with left ventricular ejection fraction < 50% or New York Heart Association (NYHA) Class III or IV heart failure (in Study 1) or NYHA Class II to IV heart failure (in Study 2) was not established because these patients were excluded from these randomized clinical trials.

Adrenocortical Insufficiency (AI): AI was reported in patients receiving abiraterone acetate in combination with corticosteroid, following an interruption of daily steroids and/or with concurrent infection or stress. Monitor patients for symptoms and signs of AI, particularly if patients are withdrawn from corticosteroids, have corticosteroid dose reductions, or experience unusual stress. Symptoms and signs of AI may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with YONSA®. Perform appropriate tests, if indicated, to confirm AI. Increased dosages of corticosteroids may be used before, during,and after stressful situations.

Hepatotoxicity: In postmarketing experience, there have been abiraterone acetate-associated severe hepatic toxicity, including fulminant hepatitis, acute liver failure and deaths. Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with YONSA®, every two weeks for the first three months of treatment and monthly thereafter. In patients with baseline moderate hepatic impairment receiving a reduced YONSA® dose of 125 mg, measure ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the ULN, or the bilirubin rises above three times the ULN, interrupt YONSA® treatment and closely monitor liver function.

Re-treatment with YONSA® at a reduced dose level may take place only after return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN.

Permanently discontinue treatment with abiraterone acetate for patients who develop a concurrent elevation of ALT greater than 3X ULN and total bilirubin greater than 2X ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation.

The safety of YONSA® re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

Based on *in vitro* data, YONSA® is a substrate of CYP3A4. In a drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. Avoid concomitant strong CYP3A4 inducers during YONSA® treatment. If a strong CYP3A4 inducer must be co-administered, increase the YONSA® dosing frequency only during the co-administration period.

Abiraterone is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8. Avoid coadministration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and considera dose reduction of the concomitant CYP2D6 substrate drug.

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone (CYP2C8 substrate) was increased by 46% when pioglitazone was given together with an abiraterone acetate single dose equivalent to YONSA® 500 mg. Therefore, patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with abiraterone acetate.

USE IN SPECIFIC POPULATIONS

- **Females and Males of Reproductive Potential: Advise male patients with female partners of reproductive potential to use effective contraception.**
- Do not use YONSA® in patients with baseline severe hepatic impairment (Child-Pugh Class C).

Please see the following page for the Brief Summary of the Full Prescribing Information.

Reference: 1. YONSA® [prescribing information]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc; May 2018.

SUN ONCOLOGY

Brief Summary of Prescribing Information for YONSA® (abiraterone acetate) tablets
This Brief Summary does not include all the information needed to use YONSA safely and effectively.
See full prescribing information for YONSA.

See package insert for full Prescribing Information
Initial U.S. approval: 2011

INDICATIONS AND USAGE:

YONSA (abiraterone acetate) is indicated in combination with methylprednisolone for the treatment of patients with metastatic castration-resistant prostate cancer.

CONTRAINDICATIONS:

YONSA is contraindicated for use in pregnant women. YONSA can cause fetal harm and potential loss of pregnancy.

DOSAGE AND ADMINISTRATION:

Recommended dose: YONSA 500 mg (four 125 mg tablets) administered orally once daily in combination with methylprednisolone 4 mg administered orally twice daily. Patients receiving YONSA should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

To avoid medication errors and overdose, be aware that YONSA tablets may have different dosing and food effects than other abiraterone acetate products.

WARNINGS AND PRECAUTIONS:

YONSA may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with YONSA.

Monitor for symptoms and signs of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations.

Hepatotoxicity can be severe and fatal. Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with YONSA, every two weeks for the first three months of treatment and monthly thereafter.

ADVERSE REACTIONS:

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

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

DRUG INTERACTIONS:

CYP3A4 Inducers: Avoid concomitant strong CYP3A4 inducers during YONSA treatment. If a strong CYP3A4 inducer must be co-administered, increase the YONSA dosing frequency.

CYP2D6 Substrates: Avoid co-administration of YONSA with CYP2D6 substrates that have a narrow therapeutic index. If an alternative treatment cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate.

USE IN SPECIFIC POPULATIONS:

Females: Women who are pregnant or women who may be pregnant should not handle YONSA tablets without protection, e.g., gloves.

Males of Reproductive Potential: Males with female partners of reproductive potential should use effective contraception.

Hepatic Impairment: Do not use YONSA in patients with baseline severe hepatic impairment (Child-Pugh Class C).

Pediatric Use: Safety and effectiveness of abiraterone acetate in pediatric patients have not been established.

To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-818-4555, FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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SUN PHARMA

Advanced PCa: How evolving treatment approaches impact patient care

Experts highlight recent clinical data and their implications for diagnosis, treatment

It's an exciting time for the management of advanced prostate cancer with several drugs now approved for the treatment of metastatic castration-sensitive, nonmetastatic castration-resistant, and metastatic castration-resistant prostate cancer. A panel of experts recently gathered to review recent data from clinical trials investigating treatments for advanced prostate cancer and discuss practical implications for patient care. Highlights of their discussion are presented here.

The panelists were moderator Raoul Concepcion, MD, director, The Comprehensive Prostate Center, and clinical associate professor of urology, Vanderbilt University School of Medicine, Nashville, TN; **Jahan Aghalar, MD,** genitourinary medical oncologist, New York Cancer & Blood Specialists, New York; **Gordon Brown, DO,** director, New Jersey Urology Center for Advanced Therapeutics, Cherry Hill, NJ, and medical director, robotic surgery, Thomas Jefferson Hospitals in Sewell, NJ; **Jorge Garcia, MD,** Kerscher Family Chair for Clinical Prostate Cancer Research and staff physician in the departments of hematology and oncology and urology, Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland; and **Paul Sieber, MD,** president and medical director of research, Lancaster Urology, Lancaster, PA.

Edited by Cheryl Guttman Krader
UT Contributing Editor


DR. CONCEPCION

DR. CONCEPCION: Patients with metastatic castration-sensitive prostate cancer (mCSPC) can be thought about as two groups. One group consists of patients who were definitively treated with radiation therapy (external beam, brachytherapy, or a combination), became lost to follow-up, and subsequently presented with widespread metastatic disease. The second group is men presenting with de novo metastatic disease, and I think there has been a shift toward seeing more of these patients because of the controversial recommendations on PSA testing and screening. These are men who never saw a urologist or had a biopsy but seek care because they are experiencing pain that is found to be associated with widespread metastatic disease.

Historically, the care process for these patients has been to do a biopsy. Then, if it is positive and the patient has metastases, androgen deprivation therapy (ADT) is started, and the patient is followed. Over the past few years, there have been multiple clinical trials that have led to the approval of other agents that can be added to ADT. Dr. Garcia, please summarize the findings from the key registration trials that are changing the paradigm for managing patients with mCSPC.

DR. GARCIA: At least for me, the standard of care for mCSPC changed dramatically with release of results from the ECOG CHAARTED trial. CHAARTED was designed to address the simple question of whether adding docetaxel-based chemotherapy to ADT upfront would prolong overall survival rather than waiting until men become castration resistant to start chemotherapy.

It is important to hone in on how patients were defined in CHAARTED. They were stratified at entry by disease volume, although most patients had high-volume disease. The data showed unequivocally that across all comers, men who received ADT and docetaxel-based chemotherapy given standard fashion, six cycles of docetaxel 75 mg/m^2 given every 3 weeks, had superior survival compared with those men who only received ADT. Subgroup analysis with patients categorized by disease volume showed that the patients who benefited the most were those with high-volume disease. In that subgroup, adding docetaxel reduced the risk of mortality by almost 40%. That is a huge reduction that changed the management paradigm for me. Now I tell my patients that volume is important, and intensification of therapy is needed.

Results from the STAMPEDE trial were reported in the same year. STAMPEDE had a very complex, multi-arm, multistage trial design. ADT was the backbone of treatment and treatment could be added that complements ADT, but then treatments could be removed or added based on interim analyses and how the field was changing.

STAMPEDE also found that adding docetaxel-based chemotherapy to ADT drastically improved survival. A subgroup analysis with patients categorized by disease volume was done post-hoc and showed that patients with both low-volume and high-volume disease benefited from the addition of docetaxel-based therapy.

Then came LATITUDE, which had results presented in 2017. LATITUDE specifically enrolled high-volume patients, although in this French study the definition was different than in the American trials. LATITUDE found that adding the androgen biosynthesis inhibitor abiraterone acetate (ZYTIGA) to ADT also drastically improved survival compared to ADT alone The hazard ratio was 0.62, showing a 38% lower risk of death when abiraterone acetate was added to ADT.

STAMPEDE, which was done in the UK, also had an arm with ADT and abiraterone acetate and found that adding abiraterone to ADT improved survival drastically.

The data from these trials has changed our standard practice. It is sad to see data from the U.S. showing that almost two-thirds of men with advanced prostate cancer or castration-sensitive or castration-naïve metastatic disease are receiving ADT alone.

DR. CONCEPCION: Thank you for that wonderful summary of the data that support adding docetaxel or abiraterone to ADT for mCSPC. There are other agents that have been approved for treating castration-resistant prostate cancer that are moving into the metastatic castration-sensitive space. Dr. Aghalar, please give us an overview of the trials investigating those drugs.

DR. AGHALAR: In the last 2 years, we've seen a handful of trials looking at other agents in the metastatic castrate-sensitive space, particularly in the TITAN trial looking at apalutamide (ERLEADA), which was initially FDA approved for the nonmetastatic castration-resistant setting.


DR. AGHALAR

There have been two large randomized trials looking at using enzalutamide (XTANDI). Those are ARCHES, published in the *Journal of Clinical Oncology* in 2019, and ENZAMET that had results presented at ASCO this past year. Although the ARCHES trial did not show an overall survival benefit for enzalutamide, many experts are confident that the data are not yet mature enough. The interim analysis did show a very significant improvement in radiograph-

ic progression-free survival (rPFS) of about 22 months (for using enzalutamide).

The ENZAMET trial showed benefit of enzalutamide in multiple parameters, and this agent is now approved for the treatment of mCSPC. In addition, we are waiting eagerly for the results of the ongoing ARASENS trial that is investigating the newest androgen receptor blocker, darolutamide (NUBEQA), for mCSPC.

Treatment of nonmetastatic CRPC

DR. CONCEPCION: Dr. Brown, please discuss the trials that have brought approvals for agents to treat patients with nonmetastatic CRPC (nmCRPC) who would be defined as men on ADT who have a testosterone level in the castration range, rising PSA, and no evidence of metastasis by traditional imaging using technetium-based bone scan and computed tomography.

DR. BROWN: Three trials investigated treatment for nmCRPC. The first was the SPARTAN trial that showed apalutamide improved metastasis-free survival (MFS) by about 24 months and reduced the risk of disease progression over time. The PROSPER trial showed a 22-month improvement in MFS with the use of enzalutamide in patients with high-risk nmCRPC. Most recently, results from the ARAMIS trial showed a 22-month improvement in MFS in patients with high-risk nmCRPC treated with darolutamide.


DR. BROWN

Now the burden rests on clinicians to find these patients in our advanced prostate cancer clinics because the available data suggest the potential for delaying progression of disease. Their use may also have a benefit for improving overall survival, but the data for that endpoint are not mature yet.

Imaging in nmCRPC

DR. CONCEPCION: It is important to understand that the men in SPARTAN, PROSPER, and ARAMIS had nonmetastatic disease based on negative bone scans and CTs. It is likely, however, that they have micrometastases, and that brings up the role of next-generation imaging.

Dr. Brown, what imaging are you using in your practice to detect metastases?

DR. BROWN: We do a CT scan and bone scan as first-line imaging. Then, because a positive scan will make a therapeutic difference for accessing available therapies, we do an ^{18}F-Fluciclovine PET/CT (Axumin) scan if the results of those tests are equivocal or if they are negative and we believe the patient is at high risk for progression. Axumin scanning is readily available in our community and covered pretty routinely by payers.

We do not do Axumin scanning routinely. That would be challenging from a cost and payer perspective.

DR. AGHALAR: We also start with a traditional CT and bone scan, but then almost unequivocally do an Axumin scan to rule out distant metastasis for patients with biochemical recurrence for whom we are considering salvage options, such as salvage radiotherapy. We are not using any other tracers outside of clinical trials, but I think the future is exciting with the potential availability of PSMA scans that may have therapeutic implications.

Use of a novel tracer may or may not impact outcomes for oligometastatic disease. What do you do if the Axumin scan in a patient with a slowly rising PSA shows one site of metastasis at L4? Do you try to ablate the metastasis with radiation, and will that impact the trajectory of the cancer? That situation raises interesting questions that will be brought up in the examination room and also hopefully in the research realm.

Emerging mCRPC treatment landscape

DR. CONCEPCION: Dr. Garcia, what developments in treatment of mCRPC are we expecting in 2020?

DR. GARCIA: Among men with prostate cancer in the United States, the incidence of germline mutations, including *ATM*, *BRCA1*, *BRCA2*, and many others, is probably less than 10%. There are also somatic changes or epigenetic changes that are DNA repair by nature, and there are data to suggest that they can be exploited therapeutically. It has been reported that men with mCRPC receiving the oral PARP inhibitor olaparib had a significant improvement in progression-free survival and also a good decline in PSA. Analyses to identify who these patients were suggested they were those who had *ATM* and *BRCA1/BRCA2* mutations, and so they were true germline mutation patients.


DR. GARCIA

That was the genesis for the PROfound trial that Dr. Maha Hussain presented at the European Society for Medical Oncology Congress in Barcelona. PROfound randomized men with progressing mCRPC to olaparib or an oral agent they had not received before. For example, a patient who had been on abiraterone for M1 CRPC who was randomized to oral therapy would be put on enzalutamide.

The important part of the randomization was that patients were selected based on the type of DNA repair deficiency they had. Cohort A included patients with *BRCA1*, *BRCA2*, and *ATM* mutations and Cohort B included patients with any other DNA repair deficiency.

The primary endpoint of this trial was for Cohort A, who were the true germline patients. The results showed for the first time a benefit for a biomarker-driven approach to treatment selection. Compared with the oral agent group, treatment with the PARP inhibitor was associated with improvements in rPFS and survival. The benefit of treatment with the PARP inhibitor was maintained in a pooled analysis of cohorts A and B, which includes all DNA repair deficiencies.

Some of us were a bit concerned as to the impact of that second cohort of patients because theirs were not *ATM*, *BRCA1*, and *BRCA2* mutations. But it appears that the hazard ratios were maintained for rPFS. We know that *BRCA1* and *BRCA2* are exquisitely sensitive to PARP inhibitors and that not all DNA repair deficiencies are responsive to PARP inhibitors. Hopefully olaparib will become available, and once it is in our hands, we are going to start teasing out exactly which patients may benefit the most from its use.

DR. CONCEPCION: Generic abiraterone acetate became available in 2019 and now we are seeing hybrids, which are approved by the FDA through a 505(b)(2) submission. Yonsa is an approved abiraterone hybrid and DRGT-45 has completed a phase I trial.

Dr. Brown, how might these drugs be beneficial to a large practice like yours that cares for a lot of patients?

DR. BROWN: The amount of support that the manufacturers of the hybrid drugs offer to us versus generic manufacturers with respect to throughput, educational materials, and a benefits perspective are all important for allowing us to get patients on a drug that is mechanistically very similar to the innovator brand and may be beneficial for that specific patient over other therapy choices.

DR. CONCEPCION: Dosing is different with the hybrid drugs compared with the original brand because they are reformulated. In Yonsa, abiraterone is ultramicronized, and so it has better bioavailability. DRGT-45, which is abiraterone acetate tablets for oral suspension, was also formulated for improved bioavailability, and it is administered as a drink rather than a pill. What role will the difference in dosing play?

DR. SIEBER: I think the situation is analogous to what we saw with medications for overactive bladder where improved formulations enabled once-daily dosing, ingestion on an empty stomach, or a lower dose. We have to remember that the typical patient being treated with these drugs for prostate cancer is a man in his 70s. Any modification that makes a treatment more convenient or better tolerated is going to have an advantage in this population of men who already have life challenges. UT


DR. SIEBER

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JA008 Rev 1/20

Surveillance safe for patients with Grade Group 1 prostate Ca

<1% risk of metastasis, prostate cancer-specific mortality in large study

BADAR M. MIAN, MD

Dr. Mian is professor of surgery in the division of urology at Albany Medical College, Albany, NY.

Active surveillance (AS) for low-risk prostate cancer is recommended as a viable or preferred option by most professional organizations, and it has gradually gained acceptance by most physicians who manage this condition. Several reports over the last two decades demonstrated the safety of AS for men with very low- or low-risk prostate cancer. An AS approach, unlike watchful waiting, still retains the option to treat, with an intention to cure, if treatment becomes necessary. The natural history of PSA-detected, early-stage prostate cancer is quite long, so long-term safety and efficacy of AS is of particular interest.

Tosoian et al report that AS in men with very low- or low-risk, Grade Group 1 prostate cancer appears to be quite safe, with risk of metastasis or prostate cancer-specific mortality (PCSM) of <1% *(Eur Urol* Jan. 6, 2020 [Epub ahead of print]). In their large, prospective AS program, 1,818 men were enrolled after the initial prostate biopsy revealed very low-risk (1,293, 71%) or low-risk (525, 29%) prostate cancer.

After enrollment, the initial monitoring protocol included repeat prostate biopsy every year. Multiparametric MRI and mpMRI/ultrasound-fusion targeted biopsy were used since 2013 and 2014, respectively. Five hundred thirty-seven men (30%) underwent pre-enrollment mpMRI, with nearly half (47%) with a positive MRI requiring image-fusion targeted biopsy.

The study enrolled 1,818 patients from January 1995 through June 2018, with 920 men followed for ≥5 years and 305 men for ≥10 years. The median interval between biopsies was 13 months. The cumulative incidence of loss to follow-up at 3, 5, and 10 years was quite low at 3%, 4%, and 6%, respectively. Definitive treatment was offered to all patients with grade reclassification (Grade Group ≥2) on any subsequent prostate biopsy. Treatment or continued AS was offered to men whose repeat biopsy showed increase in volume of cancer (more than two positive cores and/or >50% involvement of a core).

Of the entire cohort, 92 men (5%) died at a median age of 80 years, and of those, 88 were due to non-prostate cancer causes. The cumulative incidence of all-cause mortality was 6.8% at 10 years and 28% at 15 years. Death due to prostate cancer was quite rare, with only four men (0.2%) dying of prostate cancer during the study period. The cumulative incidence of PCSM or metastasis was 0.1% at both 10 and 15 years.

Seven hundred twenty-seven men (40%) underwent biopsy grade reclassification, with the 5-, 10-, and 15-year incidence of grade reclassification of 21%, 30%, and 32%, respectively. The incidence of reclassification to Grade Group ≥3 was 7%, 10%, and 11%, respectively. Of the 693 men who underwent treatment, 78% were due to biopsy reclassification while 22% were due to change in preference. The 5-, 10-, and 15-year incidence of receiving definitive treatment was 36%, 48%, and 52%, respectively.

Death due to prostate cancer was quite rare, with only four men (0.2%) dying of prostate cancer during the study period.

On multivariable analysis, pre-enrollment mpMRI was associated with a reduced risk of grade reclassification (p=.03). Factors associated with grade reclassification included older age, later year of diagnosis, African-American race, and increased PSAD, number of positive cores, and core involvement. Although the data showed that older age, African-American race, and measures of cancer volume, as well as use of pre-enrollment mpMRI were associated with an increased risk of grade reclassification, these variables did not appear to negatively impact any of the survival outcomes. There does not appear to be any strong rationale to limit African-American patients from enrolling in an AS protocol.

Because the mortality rate (overall and cancer specific) and metastases were so infrequent, the Grade Group reclassification was the most frequent outcome reported. Clearly, grade reclassification should not be viewed as an ominous event since these patients were captured through AS and treated, without negatively affecting their overall survival. Nearly 38% of patients underwent treatment, including those who had a change of heart about AS. No data are provided about the type of definitive treatment received by these patients. It would be instructive to know their pathologic outcomes, recurrence rates, or the need for secondary therapies.

Pre-enrollment mpMRI was associated with a decreased risk of biopsy grade reclassification during follow-up, especially if the mpMRI was negative. It's not clear from this study whether the mpMRI was used "during" AS and how often. It will be interesting to learn whether these patients with pre-enrollment and/or surveillance mpMRI benefitted in terms of fewer subsequent biopsy sessions or fewer cores taken.

The monitoring protocol reported by the authors is quite stringent, with frequent (annual) repeat biopsies. As active surveillance protocols for low-risk prostate cancer become more widely accepted, there are justifiable concerns about the AS-related morbidity of intensive monitoring. It's likely that a less invasive surveillance protocol, incorporating better imaging (eg, mpMRI) or genomic testing and fewer biopsies, will not adversely impact the excellent survival outcomes while making AS a more readily acceptable option for low-risk prostate cancer. UT

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Is MRI fusion Bx the new gold standard for diagnosing PCa?

DR. STROPE

"It hasn't become the gold standard yet. There are still a lot of inter-reader reliability issues. The same MRI scans, read by different radiologists, may be read differently. That's going to limit its broad application across the country as a whole and is a major issue.

Anecdotally, within our own practice we've seen that when a scan done in one facility needs to be translated for the fusion biopsy machine we utilize, we'll get a different reading from the radiologist here than from the original radiologist. There's a discrepancy between what the two radiologists see on the scan. That issue definitely needs to be worked out.

I expect some interesting data on that in the future. The PI-RADS system tries to standardize the readings, but there are still discrepancies between the different readers. Working out the readability issue will make a difference.

The gold standard is still a positive traditional biopsy, but that could evolve over the next few years.

The other issue is whether it gets broad acceptance from insurance companies. Some insurers approve it in the initial biopsy setting, but many do not. So that's going to be the next point for broad applicability.

Still, I would say we're definitely seeing an increased utilization of MRI for additional diagnosis of prostate cancer within our practice as a whole."

Seth Strope, MD / St. Louis

"We don't have MRI fusion biopsy available in our community, in our hospital, or in our office, so for an initial biopsy, we still do standard transrectal ultrasound biopsy in the office with ultrasound guidance. We may refer patients who need a second biopsy to a university center for MRI fusion for a second biopsy if they have persisting elevated PSA or other factors that are suspicious. It's just not feasible for everybody to do MRI fusion yet. For the majority of urologists, it's still not even commercially available.

DR. EISENBERG

Even if it were available, I'm not sure it would be our first choice yet. The yield is a little bit better, but our percentage yield of positive biopsies is pretty close to MRI fusion biopsies, at least in our practice. Our results differ by just 5% to 10%—not much.

I don't think they're necessary for everybody. As I said, we use them when we're puzzled, when men have already had two or three biopsies, and we see them for consultations. In those situations, MRI fusion is a good next step."

Robert Eisenberg, MD / Modesto, CA

"That's a great question. At our center, probably 80% of biopsies are done the traditional way with a transrectal ultrasound-guided approach.

Practice patterns in our area and insurance coverage usually dictate that the patient with an elevated PSA who needs a first-time biopsy is not able to get an MRI covered by insurance. That may change over the next couple years, but now most initial biopsies are done the standard way.

DR. MOUL

I am still skeptical about MRI fusion because MRI quality varies so much nationwide.

A regular biopsy certainly is more efficient, less expensive, and takes less time in the urologist's office. Fusion biopsy generally takes about twice as long as a standard biopsy. Fusion biopsies could easily create issues of having enough providers, nurses, and rooms to do all biopsies in a fusion manner on every patient with an elevated PSA. It's resource intensive and expensive.

We initiated an important program with our primary care doctors to do a better job identifying younger men with elevated PSA, high-risk men, such as African-American men, and men with a family history of prostate cancer. That's increased the number of men who need biopsies at our center.

I'd rather focus on reaching underserved men and not be totally swept away by the MRI craze, especially since some recent data shows that results from initial MRI fusion biopsies can vary greatly, even in clearly high-grade cases."

Judd Moul, MD / Durham, NC

Letters /

We welcome letters to the editor.
Please send correspondence to **urology_times@mmhgroup.com.**

It's high time for men to be screened for prostate Ca

To the editor:

The interview with Dr. Kelvin Moses on prostate cancer (PCa) in African-American (AA) men rightly points out that AA men are in a high risk group as they have pro PCa genetic factors and hence AA need to be screened and maintain regular follow up care for PCa ("Addressing prostate cancer's racial disparity starts with you," February 2020, page 18).

In the two decades (1990 to 2012), due to PSA and digital rectal examination (DRE) screening, the PCa mortality was reduced by 50%. It is only after the U.S. Preventive Services Task Force (USPSTF) 2012 guidelines, which provided a grade D to PCa screening, that PCa screening markedly decreased. In 2018, the USPSTF provided a grade C for PCa screening.

Today, some 50% of primary care physicians do not offer PCa screening. This has resulted in more PCa patients, more patients with metastasis, more deaths due to PCa, and higher cost of PCa care. As per the American Cancer Society, in 2020 compared to 2017, there will be 30,570 more cases of PCa and 6,600 more deaths due to PCa. CMS (Medicare and Medicaid) spent $11.8 billion in 2010 on PCa and $15.3 billion in 2018.

In the last 5 years, we have published six papers and ten letters to the editor in the U.S. urology journals and *Urology Times* favoring annual PSA- and DRE-based PCa screening. A review of 2,086 consecutive prostate biopsies in our Washington, DC region, with 70% from AA men, showed that in 2018 (post-2012 USPSTF screening guidelines), the annual prostate biopsy rate decreased by 32% but the annual PCa detection rate increased by 31%. High-grade cases increased by 9%.

In another study of 5,100 men aged 70-80 years, 61% had high-grade PCa. We have provided evidence (both from our studies and published U.S. studies) for an annual PCa screening to decrease PCa morbidity and mortality. In January 2020, we appealed to the USPSTF to present our data, but the USPSTF rejected our offer. We have suggested that AA men and men with a family history of PCa be screened annually from age 50 years and average-risk men from 55 years onward and especially healthy men 70-80 years old. Men with significant comorbidity should be counseled by their primary care doctors.

It is high time that urologists demand an annual PCa screening based on the present U.S. literature. European and UK studies have less than 1% of Black patients, while in the U.S. it is about 12% overall and in large U.S. cities, over 50%.

Sincerely,
Navin Shah, MD, and Vladimir Ioffe, MD / Greenbelt, MD

USC University of Southern California

USC Urology – *Scientific Highlights*

Lancet Oncology

Web Search Queries and Prostate Cancer: The Thin Line Between the Digital and Real World

Cacciamani G, Gill K, Gill IS. Lancet Oncology (April 2020)

We investigated the correlation between online Google searches-engine queries (SEQs) for PCa and metastatic PCa and its epidemiologic prevalence and variations according to U.S. Preventive Service Task Force (USPSTF) screening recommendations. SEQ trends correlate temporally and geographically with annual incidence of PCa, mPCa and PCa-mortality. This correlation increased further since the USPSTF recommendations (Fig.1a). U.S. state-by-state differences in SEQs reflect PCa-specific mortality in those states (Fig.1b). **Conclusion**: SEQs are a valid PCa-related public information resource and might serve as a complementary epidemiological tool. Providing accurate PCa-specific online information can deliver a valuable population-level service for patients and those related to them.

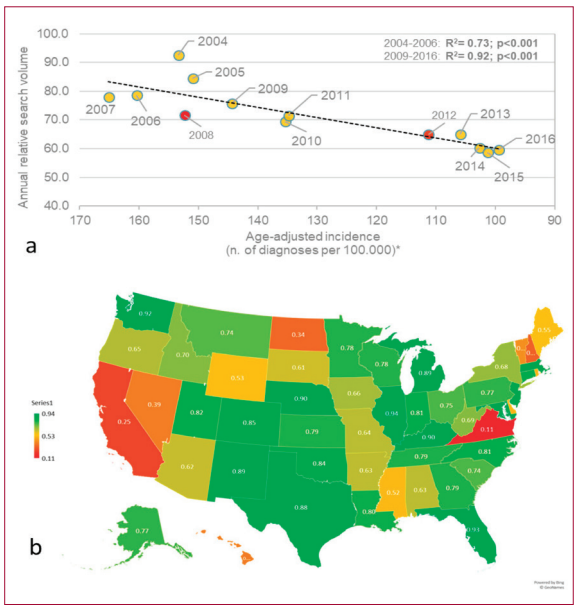


Fig 1 (a). Linear correlation between annual relative search volume (ARSV) and age-adjusted PCa incidence in the U.S.; two red dots reflect the 2008 and 2012 USPFTF recommendations.

Fig 1 (b) Heat-map chart showing U.S. state-by-state correlation between Google ARSV and age-adjusted PCa incidence (2009-2016). Epidemiological data from CDC, NPCR and NCI-SEER.

Andrologia

Opioid Prescription Patterns and Opioid Usage after Vasectomy

Asanad K, Nusbaum D, Samplaski M. Andrologia, in press 2020.

We determined urologists' opioid prescribing (e-survey) and patients' post-vasectomy pain control regimens (telephone survey). 52% of urologists routinely prescribed opioids post-vasectomy; yet, 42% of men did not actually use them. Of men using opioids, 53% used ibuprofen as their primary pain med vs 93% of men not using opioids (p=0.004). Ibuprofen use correlated with using fewer opioid tablets (p=0.003). **Conclusion**: Opioid prescription after vasectomy is common, yet not routinely necessary. Patients using ibuprofen used less opioids.

British J. Urol. International

Deep Learning on Automated Performance Metrics (APMs) and Clinical Features to Predict Urinary Continence Recovery after Robot-assisted Radical Prostatectomy (RRP)

Hung AJ, Chen J, Ghodoussipour S, Oh P, Liu Z, Nguyen J, Purushotham S, Gill I, Liu Y. BJU Int. 2019;124: 487

We predicted continence recovery in 100 RRPs using a trained deep learning (DL) model (DeepSurv). For 8 surgeons, robotic APMs were captured prospectively and compared to their historical RRPs (01/2015-08/2016). DeepSurv model features, ranked per importance in prediction, selected the top 4 surgeons "Group 1/APMs" versus others "Group 2/APMs". Continence rate: 79% @ 3 mos. Continence prediction by the DL model: CI 0.6; MAE 85.9. This model ranked APMs higher than patient features. In the historical cohort, "Group 1/APM" patients had superior continence @ 3 mos (p=0.034) and 6 mos (p=0.047). **Conclusions**: Using APMs and patient data, the DeepSurv model was able to predict continence after RRP. Surgeons with more efficient APMs had higher continence rates.

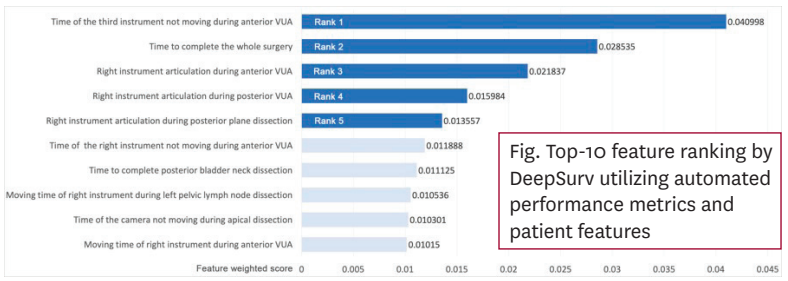
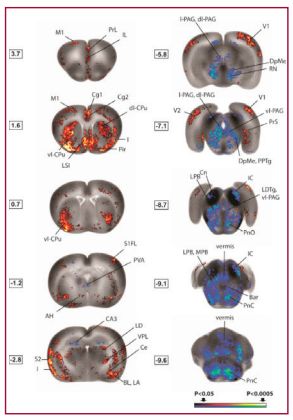


Fig. Top-10 feature ranking by DeepSurv utilizing automated performance metrics and patient features

Physiology & Behavior

Exercise Modulates Neuronal Activation in The Micturition Circuit: The MAPP Research Network Study

Daniel T, Holschneider P, Wang Z, Guo Y, Sanford M, Yeh J, Mao J, Zhang R, Rodriguez L. Physiology & Behavior 2020; 215, 112796



Stress exacerbates and exercise may improve symptoms of interstitial cystitis/bladder pain syndrome (IC/BPS). Animals exposed to water avoidance stress (WAS) have increased engagement of the brain micturition circuit. We evaluated the effect of voluntary exercise on the central amplification of stress- induced bladder hyperalgesia. After 10 days of WAS, W-K female rats were randomized to observation or daily exercise. Exercise animals had reduced bladder hypersensitivity, pain and frequency, with dose response. These changes correlated with brain changes in the micturition circuit (Barrington nucleus) and its control, the Periaqueductal Gray and the limbic system. **Conclusion**: Chronic exercise may help modify urinary symptoms in patients with IC/BPS.

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How to assess minimally invasive therapies for BPH

New treatments improve flow rate, catheter time, but 'there's work to be done'

Minimally invasive surgical therapies for BPH have seen a resurgence in recent years, but whether a single treatment modality meets all of the criteria for an "ideal" procedure remains a question. Kevin McVary, MD, of Loyola University Medical Center in Maywood, IL, provides urologists with tips on how to assess the adoptability of these treatments.

Richard R. Kerr
Content Channel Director

Q: How can urologists best assess minimally invasive therapies for the treatment of BPH?

A: Minimally invasive therapies, or MISTs, are very popular again. There was a period of time of increased popularity, that popularity dropped precipitously, and now there's a resurgence.

Why did they lose popularity and why are they having it now? They lost popularity in the past primarily because of lack of durability. A high percentage of patients asked for retreatment, sometimes in a very short period of time. There were some studies that showed more durability, but nearly uniformly, those reports showed that the impact on symptoms was not substantial. Many of these men ended up going back on medication or on to a more formal surgical approach.

As we turn the clock forward, new technologies have been introduced. So urologists have taken a cautious step back and are saying, "Are these just another prostatic gizmo?" I could give you a list, probably in the mid-20s, of devices that came on board and then left because they didn't work or they didn't work for very long.

Many urologists feel that important criteria, not comprehensive but important criteria, to evaluate are: Number one, is the technology impactful on three or four things that patients care about? is it improving their symptoms? Are the patient-reported outcomes impactful? Second, as urologists, are we improving flow rate—something that we look at as impacting prostatic obstruction? It's a more objective measure of impact. Third is the impact on important aspects like sexual function. Are they impacting erection? Are they impacting ejaculation?

"Minimally invasive therapies, or MISTs, are very popular again. There was a period of time of increased popularity, that popularity dropped precipitously, and now there's a resurgence."

KEVIN McVARY, MD

Another important aspect is generalizability. If you do it in a trial, it works at a certain level. And as you transition from clinical research into general practice, does that translate in a parallel fashion? Is it equal? Is it generalizable? Or is it only in a study patient cohort?

In my own view, durability is one question that we need to answer uniformly across the field. Are patients being impacted successfully? Then over time, is there any erosion in that durability? And are we judging durability uniformly? Unfortunately, we do not have an internationally accepted definition of durability, but we're working toward one. Right now it's not there, so in some ways, it's technology defined.

Most urologists would say, not only does the technology need to help symptoms and not at the cost of an impact on sexual function, but can it be done in the office? That's usually a good cost savings for our health system. And can it be done with a minimum amount of Foley catheter drainage or no catheter drainage at all? We have technologies that can be hugely impactful on lower urinary tract symptoms—the standard TURP or laser therapies—but those require nearly uniformly longer term catheter use afterwards. Patients perceive that as a big negative.

If MISTs are going to make a big difference, then part of that acceptance to patients is, minimize the impact on my getting back to life. That catheter time really reflects, how soon can I get back to work? How soon can I resume my hobbies, my physical activity, my golf? How soon can I resume sexual activities? Those are the major hallmarks in terms of acceptability or adoptability of MIST therapies.

Q: Do any of the current therapies meet all of these criteria?

A: In my own view, the various players don't meet all of them. They all have some aspects where there's work to be done. Maybe the technologies could be done on a slightly modified cohort, or maybe the technologies could be done in a slightly different way to minimize things like catheter time or impact on sexual function. Unfortunately, none of them are actually there yet, although we're certainly better now than we were 10 years ago. UT

REAL-WORLD AQUABLATION STUDY REPLICATES OUTCOMES OF CLINICAL TRIALS

PROCEPT BioRobotics Corp. announced that the safety and efficacy outcomes from a multicenter study of Aquablation therapy replicated those achieved in its pivotal clinical trials.

Aquablation therapy is a procedure for the treatment of BPH and is performed by the AquaBeam Robotic System.

OPEN WATER was a prospective, multicenter, single-arm, open-label clinical trial of the Aquablation procedure. One hundred and seventy-eight men with prostates sized between 20 cc and 150 cc were enrolled between September 2017 and December 2018 across five locations.

The study data, which were published in the *Journal of Clinical Medicine* (2020; 9:603), demonstrated large improvements at 12 months in symptom relief and peak urinary flow rates while preserving sexual function and urinary continence, PROCEPT BioRobotics said in a statement. Similar levels of symptom relief were seen independent of surgical experience. Moreover, the authors reported that no patient underwent a secondary procedure for recurrent BPH symptoms.

"As noted in our paper, the OPEN WATER study results indicate that the Aquablation procedure provides high levels of symptom relief, consistent with most resective techniques, but with an approximately eight times lower impact on sexual function," said lead author Prof. Thorsten Bach, of Asklepios Westklinikum Hamburg-Rissen in Hamburg, Germany.

"The magnitude of symptom relief combined with such low rates of sexual dysfunction should give confidence to every urologist considering the adoption of Aquablation therapy in his or her practice," Dr. Bach added.

What is GAINSWave ?

Advocacy

What is GAINSWave®?

A short answer might be GAINSWave is an entity created to advocate for the efficacy of shockwave therapy for the treatment of erectile dysfunction. A slightly longer answer is GAINSWave is a marketing company that was designed and built to be a platform to educate consumers about shockwave therapy and assist doctors who would like to provide a new solution to their patients. Although not a perfect solution for ED by any means, we know for some men GAINSWave therapy offers a safe, noninvasive option to surgery or medication.

As part of our advocacy, we've worked with doctors and medical professionals to develop an effective protocol based upon an existing technology that had previously been overlooked. This worked in concert with our marketing efforts, which initially sought to raise awareness about this valuable alternative.

In time, our choice to invest in advocacy has been fruitful. Because our focus is to ultimately achieve a positive outcome for both the patient and the provider, interest and adoption by physicians and patients has grown year-over-year since our launch. Consumer demand has since established GAINSWave as the industry leader for shockwave therapy for ED.

A Turnkey Solution

For physicians, GAINSWave provides a turnkey, direct-pay brand that has been successful in helping our network of providers easily add an additional revenue stream to their practices. A particularly powerful tool for edifying a solo practitioner's or small practice's independence, GAINSWave's business-in-a-box deployment can augment existing services for virtually any medical practice.

For those affected by Google's recent policy changes for medical marketing, GAINSWave offers a secure, in-demand solution complete with a host of products and services carefully designed and crafted to help our providers succeed. Everything from pricing strategy to marketing materials to videos and even commercials are provided. Most of which is updated monthly.

Additionally, we provide several valuable resources focused on helping physicians build a marketing base that can be deployed to other parts of their practice. Our online university contains instructional content covering topics such as email marketing, SEO, PPC, social media and more. Providers also gain access to a library of sales scripts, email templates and other supplemental marketing material for their practices.

Within the provider portal, members also have access to a variety of sales and marketing collateral including sales tools, patient presentations, print shop and more. GAINSWave also hosts weekly webinars and podcasts with industry leaders who provide valuable guidance, instruction and support in the form of in-depth Q&A's.

Our comprehensive onboarding procedure includes one-on-one sessions, where our team walks new providers through the support and training they will need to grow successfully with GAINSWave. These sessions cover everything from how to set up an individual directory listing to where to go to get medical questions answered. Our self-paced training session is great for helping a provider get started with GAINSWave, but since we also understand it takes more than a good first step, we've made regular support one of our primary operational goals.

As the industry leader in shockwave therapy for erectile dysfunction, we believe that Our brand only grows and becomes stronger when Your brand grows and becomes stronger. We support and encourage our providers to develop and strengthen their brand by using the valuable tools we provide within our portal to raise the profile of other aspects of their practice. This, in addition to our national marketing efforts, make it possible for providers to grow their profiles on local, regional and even national stages to help educate the public about treating erectile dysfunction with GAINSWave.

Having the resources and support of an entire marketing company gives each GAINSWave provider the ability to quickly and easily leverage powerful marketing and proven sales techniques to improve their practice's annual hybrid revenue.

Support

If a member of our network needs patient materials such as brochures and posters or is interested in media opportunities including television, podcasting and radio, our team is continuously working with each provider to help them realize their goals. Sometimes that takes the form of additional one-on-one sessions, but for those who just want a jump on the competition, we offer a 2-day, skill-intensive workshop that has been carefully designed to help any doctor grow their practice.

"GAINSWave has given me an alternative treatment in my toolbox for patients. It's non-invasive and has no side effects and if provided to the right patient I can restore their ED without medications. So far, I've been able to help over 300 men by using GAINSWave"

—Urologist, Dr. Bruce Sloan, Philadelphia Urology Association

These workshops are led by the key opinion leaders in marketing, sales and business operations and provide proven, straightforward strategies and techniques for stimulating practice growth and for eliminating inefficiencies that may not be contributing to their goals. By opening your practice to both insurance and direct pay, you can quickly begin to develop a dynamic, hybrid practice with steady growth thanks to the strength of the GAINSWave name.

Value

For many of our providers, being able to quickly deploy a turn-key solution is a valuable benefit. Starting from day-one, our providers benefit from an established and popular brand name, an effective national pricing strategy, as well as marketing collateral and support. GAINSWave members can instantly improve their search results by adding a service to their portfolio that generates 11 times more queries than the generic term "shockwave therapy."

"I've been offering GAINSWave in my practice for over a year now. Our experience has been amazing! It's a treatment that works incredibly well and is very well received by our patients. The patients have sought us out, primarily due to the marketing efforts and through the support of GW themselves. It's truly been a boon to our patients as well as our practice."

—Urologist, Dr. Lamia Gabal, Prestige Medical Group

It is also because of these efforts that consumer interest in shockwave therapy across the board has risen steadily over the past few years. As interest in shockwave and GAINSWave therapy has grown, so too has misinformation and confusion about the efficacy of and patient selection. That is why we have partnered with Board-Certified Urologist, Dr. Judson Brandeis who has created the largest study on shockwave therapy.

SWEET Study and Continuing Education

As advocates for GAINSWave in the treatment of ED, we are committed to advancing the clinical science and protocol development for Low-Intensity Extracorporeal Shock Wave Therapy. Under the leadership of Dr. Brandeis, 40 GAINSWave providers around North America are participating in the SWEET (Shock Wave Erectile Enhancement Trial) Study.

Men are surveyed prior to treatment, upon completion of treatment, and then again every three months. GAINSWave hopes to help the Urology and Sexual Medicine community refine the protocols used to guide treatment with LI-ESWT and to determine the long-term maintenance plan.

Our commitment to education is also of prime importance to us. Dr. Brandeis hosts a bi-monthly journal review workshop where providers connect regularly to discuss trends, review articles and talk about advances in the field of male sexual health and wellbeing. During these sessions, members cover a host of topics, but recent topics have included Peyronie's Disease, Platelet Rich Plasma, Stem Cells, Vacuum Devices and the Biochemistry of erectile function to name but a few. Participation and membership in this group is exclusive and limited to GAINSWave providers.

Community

Another benefit GAINSWave providers enjoy is a robust and active community through which they can share ideas and ask questions away from the eyes of patients. Within these communities, our providers are able to connect directly with one another and discuss the issues affecting their practices in real time. Providers also use this community to share feedback and insight to help educate more patients about erectile dysfunction, the impacts it can have on their lives and how it can be treated with the help of dedicated specialists.

Our Invitation to You

This year alone, more than 30 million men will seek treatment for erectile dysfunction in the US, many of them seeking a safe, nonsurgical solution with positive, long-lasting results. While we know GAINSWave may not be the perfect fit for all men, we do know for some, it provides a noninvasive option for treating ED long-term without having to rearrange schedules or plan for recovery.

So, what is GAINSWave? GAINSWave is the key to unlocking the outcomes your patients desire while delivering the revenue you deserve. If you would like to add a therapy to your practice that will improve the lives of those you treat, or if you want to improve how you connect with your leads and patients, or if you simply want to drive repeat patronage, then I invite you to give us a call at (855) 383-5779 or visit *gainswave.com/providers* today.

Unhealthy diet associated with poor semen quality

Lowest total median sperm count seen in men consuming Western diet

Lisette Hilton
UT Correspondent

Unhealthy eating, like that associated with the Western diet, is associated with notably worse semen quality and less favorable testicular function than healthier eating patterns, according to a study of nearly 3,000 young Danish men published in *JAMA Network Open* (2020; 3:e1921610).

Researchers at Harvard T.H. Chan School of Public Health, Boston performed a cross-sectional study of men in Denmark (median age, 19 to 20 years) who didn't know their fertility status and had filled out a validated food frequency questionnaire. The authors assessed semen quality and concentrations of total and free testosterone, estradiol, inhibin B, follicle-stimulating hormone, luteinizing hormone, and sex hormone-binding globulin. They also studied testicular volume.

"This study is the largest study to date to examine diet pattern with men's testicular function," said study co-author Feiby Nassan, ScD, MBBCH, MSc, a research associate at the Harvard T.H. Chan School of Public Health who worked on the study with Niels Jørgensen, MD, PhD, and colleagues.

Decline of semen quality is a growing concern in men around the world. Total sperm count among men in Western countries fell by 50% to 60% from 1973 to 2011, according to a meta-analysis of 185 studies published in *Human Reproduction Update* (2017; 23:646-59).

Why this is happening is a topic of debate. And while authors are looking at environmental exposures, such as pollution, and behavioral factors, such as smoking and alcohol consumption, they say few have looked at diet quality as a possible cause.

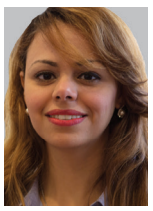
Dr. Nassan and colleagues identified four popular dietary patterns: the largely unhealthy Western diet, with staples such as pizza, processed and red meats, refined grains, and sweets; the generally healthy prudent diet, emphasizing fish, chicken, vegetables, fruit, and water; the traditional Danish open-sandwich pattern, featuring consumption of cold, processed meats, whole grains, mayonnaise, cold fish, condiments, and dairy; and a vegetarian-like pattern, which avoids red meat and chicken and emphasizes vegetables, soy milk, and eggs.

They found that men consuming a Western diet had the lowest total median sperm count at 122 million. Men consuming foods associated with the prudent pattern had the highest median total sperm count at 167. Median sperm counts were 151 million for the vegetarian-like and 146 for the open-sandwich patterns.

> Men consuming foods associated with the prudent pattern had the **highest median total sperm count at 167.**

Average sperm counts varied within the categories. For example, men in the highest quintile of Western diet consumers had an average 26 million sperm count lower than men in the lowest quintile of Western diet eaters. And those that adhered most to the prudent pattern, the highest quintile, had an average 43 million more sperm than prudent eaters in the lowest quintile.

"This study provides some evidence of the benefits of the generally healthy diet patterns that you could advise your patients to follow—especially the ones whose fertility may need a nudge and may benefit from such diets."



FEIBY NASSAN, ScD, MBBCH, MSc

Men who highly adhered to the open-sandwich pattern had higher counts of motile spermatozoa, while those who consumed a vegetarian-like pattern were more likely to have more morphologically normal spermatozoa compared to men in other dietary categories. Further, men in the highest quintile of Western diet consumers had lower serum inhibin B concentrations and ratios of inhibin B to follicle-stimulating hormone than men in the lowest quintile of Western diet eaters.

Hormone results 'difficult to explain'

"The hormone results are difficult to explain. Men who had the highest adherence to the Western pattern had higher testosterone concentrations, compared with men with less adherence. But they also had the highest estradiol concentration with unchanged luteinizing hormone levels," Dr. Nassan said. "This could be due to increased aromatization of testosterone to estradiol and could have resulted in increased negative feedback at the hypothalamic level. If this is correct, this might also explain why follicle-stimulating hormone was not sufficiently higher as a compensation for the lower inhibin B concentration."

The authors speculated that adherence to the Western diet pattern, at least in part, could lead to reduced hypothalamic activity, which could explain the observed reduction in spermatogenesis, according to Dr. Nassan.

"In addition to this possible explanation, the lower ratio of inhibin B to follicle-stimulating hormone, itself, could also explain a direct adverse effect on the testicles," she said.

A take-home for urologists, according to Dr. Nassan, is that it may be useful for men's fertility to follow a generally healthy diet with higher intake of fish, chicken, vegetables, fruit, and water, while cutting back on pizza, French fries, processed and red meats, snacks, refined grains, high-energy drinks, and sweets.

"Patients usually come to your clinics asking those questions about what they should eat and what they should avoid to boost their fertility. Peer-reviewed evidence is limited to answer these questions. This study provides some evidence of the benefits of the generally healthy diet patterns that you could advise your patients to follow—especially the ones whose fertility may need a nudge and may benefit from such diets," she said.

A limitation of the study is its cross-sectional design, as the authors cannot imply causation from the work.

"However, this does not mean that this association is not important. Many scientific groups, including ours, are working to further study the role of diet and environment on fertility. However, I do not think we have to wait until the perfect controlled blinded clinical trial to happen until we change behavior. In addition, many other studies have suggested consistent results with other health outcomes, so we really have little or nothing to lose if we follow a generally healthy diet," Dr. Nassan said. UT

Thulium laser shows several advantages

Greater flexibility seen with thulium technology vs. holmium:YAG laser lithotripsy

Lisette Hilton
UT Correspondent

U.S. academic centers using the SuperPulse Thulium Fiber (SPTF) laser to treat stones are finding it offers several advantages compared with holmium:YAG laser lithotripsy. But more research comparing the two is needed, according to a presentation at the 2019 World Congress of Endourology and SWL in Abu Dhabi, United Arab Emirates.

The SPTF is a new lithotripsy platform. It is different than holmium:YAG laser technology, which urologists have used for more than 20 years to treat kidney stones, according to presenting author Wilson Molina, MD, professor of urology and director of the Kidney Stone Disease Program at the University of Kansas Medical Center, Kansas City.

Whereas holmium:YAG laser lithotripsy typically uses 200-µm to 365-µm optical laser fibers, the thulium laser allows the use of 150-µm core-sized fibers. Dr. Molina, along with urologist colleagues from Ohio State University, Columbus, presented a comparison of lithotripsy with a 242-µm core-sized fiber holmium:YAG (AccuMax 200), to the 150-µm core-sized SPTF.

"The thulium platform has an advantage compared to the holmium:YAG in that it's a portable system, which urologists can plug into a 120-volt outlet. If you can plug in your cell phone, you can plug in the machine," Dr. Molina said.

Another advantage of the new technology, which the FDA cleared in August 2019, is that it isn't noisy, according to Dr. Molina.

The thulium offers laser settings that the holmium does not, including high-frequency settings up to 2000 Hz. Urologists could use the thulium for dusting or fragmenting kidney stones, Dr. Molina said.

Thulium laser highly absorbed by water

In theory, the thulium technology should be a more effective stone treatment because the laser is highly absorbed by water.

"It's a laser of 1,940 nm of wavelength, which is at the tip of the curve for water absorption. For that reason, it is probably more effective than the holmium laser," he said.

Because the profile of the beam generated by the SPTF is smaller than the beam profile created by the holmium laser, the SPTF can use smaller laser fibers—as low as 50 µm. The holmium laser can only use fibers greater than 200 µm.

"There are three advantages of using smaller fibers. Number one, smaller fibers allow the ureteroscopes to have a better flexion in order to navigate inside the kidney easier. The Olympus 150 SuperPulse Thulium Fiber [laser] has greater flexibility and is able to bend to a tighter diameter before thermal breakdown compared to the AccuMax 200. Number two, with small fibers, we have better irrigation during the procedure with better visualization. Third, it potentially delivers energy in a smaller area of the stone, creating fragments that are smaller dust-type fragments," Dr. Molina said.

Nearly all patients with kidney stones who can be treated with an endoscopic retrograde approach would benefit from the new technology.

"I think this laser could be used for a retrograde approach in patients that have larger stones that cannot undergo the percutaneous approach for reasons such as other comorbidities because it has the potential to be faster in terms of breaking up the stones," Dr. Molina said.

The drawback to using the SPTF is that it's a new technology that doesn't yet have consistent clinical data. In the United States, only three academic sites have used SPTF laser lithotripsy since early October 2019, according to Dr. Molina.

"There is some long-term clinical data from a similar technology abroad that is promising. But until we have long-term clinical data that compares with the holmium laser, we cannot make any consistent evaluation," Dr. Molina said.

Dr. Molina and colleagues have submitted an abstract of the first 25 cases detailing use of the laser to perform the retrograde approach, but it is not yet published. He said researchers have shown so far that the thulium laser is feasible to use and is safe for patients.

Dr. Molina helped to develop the SuperPulse Thulium Fiber laser and is a consultant for Olympus. UT

SECTION EDITOR
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New developments may change treatment of OAB

β-agonist, PTNS devices may soon offer more options for improving QoL

NATHAN CHERTACK, MD; GARY LEMACK, MD

Dr. Chertack is a urology resident and **Dr. Lemack** is professor of urology and neurology, UT Southwestern Medical Center, Dallas.
Disclosure: Dr. Lemack serves on the clinical events committee for Blue Wind Medical and is a clinical investigator for StimGuard.

Overactive bladder (OAB) syndrome affects millions of individuals worldwide, with as many as 20% of the population affected. Current American Urological Association/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction guidelines suggest a stepwise approach to management, starting with conservative strategies (behavioral modification and pelvic floor treatments), adding medications when needed (eg, anticholinergic and β-agonist medications), and moving on to advanced therapies (eg, onabotulinumtoxinA [Botox] detrusor injections as well as sacral and percutaneous neuromodulation) if less invasive strategies are ineffective or poorly tolerated.

New treatments (pharmacological and device based) are currently in development to expand our OAB armamentarium.

Drug therapy: β-agonists

The bladder receives both sympathetic (β-receptors—primarily relaxant) and parasympathetic (muscarinic receptors—primarily excitatory) innervation. Medical therapies may be directed at either to combat OAB, with antimuscarinics having been the mainstay of treatment for years. Mirabegron (Myrbetriq) is currently the only β-agonist available for the treatment of OAB and is generally well tolerated. Initial concerns for hypertension were not noted in the registration trials, though patients with poorly controlled hypertension should not be treated with this class of medications.

Vibegron is a new β-agonist currently in phase III clinical trials; its new drug application was recently accepted by the FDA. Initially developed for obesity treatment in the 1990s, it was found to improve OAB symptoms.[1] Unlike mirabegron, it has no cytochrome P450 enzyme interactions.

Yoshida et al initially examined the efficacy of vibegron (both 50 mg and 100 mg) over a 12-week time frame and found that patients on vibegron demonstrated significant improvement in micturition frequency, daily urgency episodes, daily incontinence episodes, nocturia episodes, and volume per void when compared with placebo.[2] Treatment effects were seen within 3 weeks of starting therapy. More than 90% of patients reported satisfaction after a vibegron treatment course, with adverse events (AEs) similar to placebo. Additional analyses revealed an improvement in nocturia and, as one would expect, an improved AE profile with regard to xerostomia in a comparative trial with tolterodine.[3,4]

Tibial neuromodulation

Percutaneous tibial nerve stimulation (PTNS) was developed and approved in the early 2000s, when it was demonstrated that weekly low-level electrical stimulation of the tibial nerve utilizing an acupuncture needle improved patient-reported OAB symptoms.[5] Despite its benefits, PTNS requires frequent clinic visits (30-minute sessions weekly for 12 weeks, then typically every 4-8 weeks maintenance) and, in part, because of this schedule, has not been widely embraced. Additionally, the improvements in urge incontinence following PTNS do not appear to be as robust as with either onabotulinumtoxinA or sacral neuromodulation.

The concept of implantable tibial nerve stimulators is not new, with the Urgent-SQ developed in 2006 and 9-year results reported in 2013.[6] However, the device was never manufactured or marketed and no further study results were reported.[7] Recently, mul-

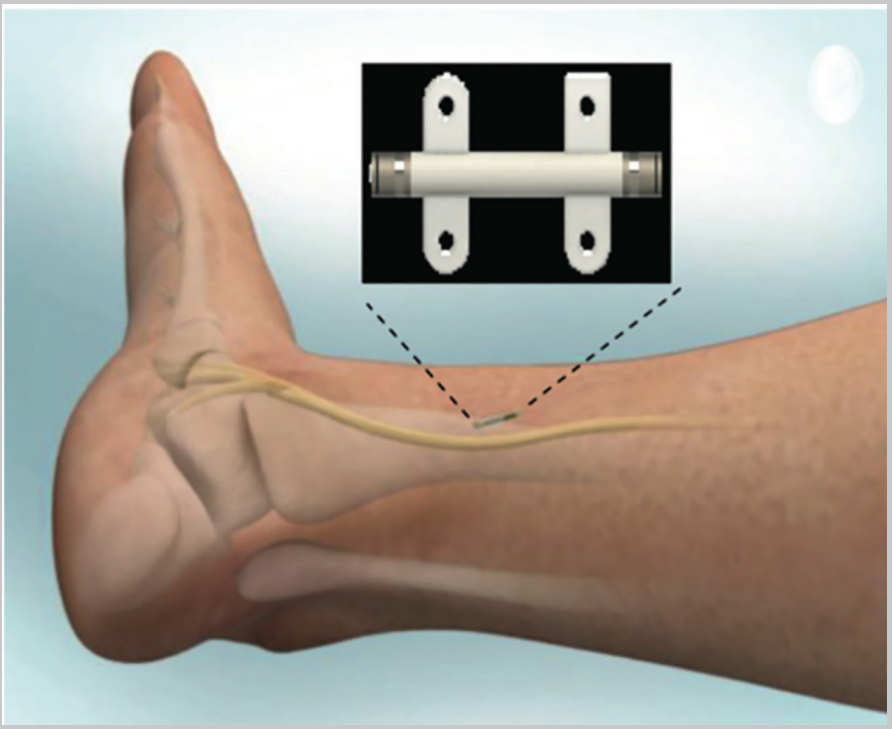

FIGURE 1 / Renova device and implant location. *(Reproduced with permission from J Urol 2017; 198:205-10)*

tiple companies have piloted implantable tibial neurostimulators in the hopes of bypassing the shortcomings of PTNS.

RENOVA (BlueWind Medical) is one such implantable device. A short (<45-minute) clinic-based procedure is required to place the 25-mm device next to the tibial nerve, just proximal to the medial malleolus through a 5-cm incision (figure 1). The device does not require batteries and is powered by an external control unit that is worn on the ankle only during treatments. An initial study that followed 15 patients for 3 months after implantation[8] noted decreased void frequency, increased voided volume, and decreased episodes of urgency and urge incontinence. No complications were noted and patients reported no issues with operating the control unit.

A later study of 34 patients treated over 6 months demonstrated clinical success (>50% improvement in one or more study outcomes) in 67% of patients and no incontinence episodes in 28%. Almost half (47%) of patients reported acute AEs (mostly implant site pain, suspected wound infection). Three-year data from this initial cohort suggest long-term efficacy (success in >75% of patients) and diminished AE profile.[9]

Another device currently in development is the eCoin. A short (<20-minute) clinic-based procedure is performed under local anesthesia to implant the nickel-sized device into the medial lower leg (figure 2). The device is automatically set to provide stimulation every other day for 2 weeks, then twice per month.

Forty-six patients were implanted with the device and followed for 6 months.[10] After activation, patients noted a 71% median reduction in the number of urge incontinence episodes at 12 weeks. Overall, 24% reported no urge incontinence episodes at 6 months. No patients required device revision or removal during the study, although one patient developed cellulitis and one patient developed device migration after vigorous exercise. Recent data suggest that efficacy has been maintained at 1 year following implantation.[11]

Two other tibial stimulation devices are currently in the early stages of development for OAB therapy. StimRouter consists of an implantable lead and a wireless control device. It has been shown to be efficacious in the treatment of patients with peripheral nerve pain and is currently being studied for OAB treatment.[12,13] CAN-Stim also consists of an implantable lead and wireless control device. Patients are currently being enrolled in trials for comparison between implantable tibial and sacral neuromodulation.[14]

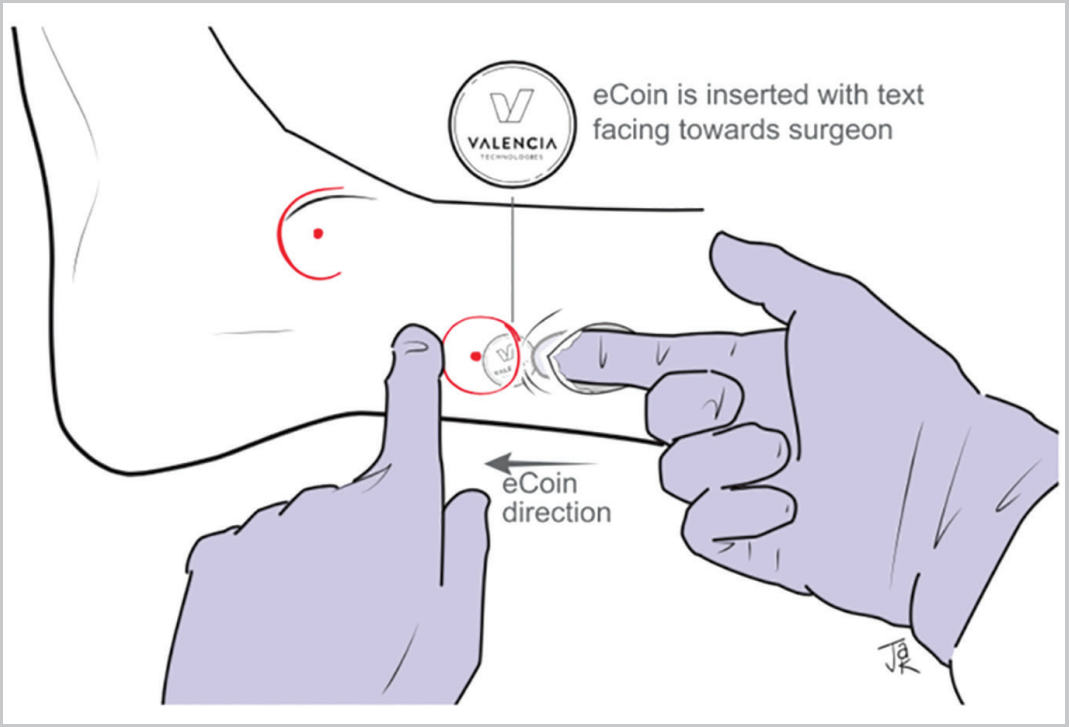

FIGURE 2 / eCoin device and implant location. *(Reproduced with permission from J Urol 2017; 198:205-10)*

Conclusions

OAB syndrome is a widely prevalent disorder with a multitude of treatment options. Antimuscarinic medications may result in undesired side effects or lack of treatment efficacy, and overall, patients only uncommonly stay on medications long term. The development of vibegron as an alternative β-agonist and a variety of implantable tibial neurostimulators may soon offer patients with OAB a wider array of options for improving quality of life. UT

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How to code for urologic care during the COVID-19 pandemic

Medicare relaxes several telemedicine provision/billing requirements

JONATHAN RUBENSTEIN, MD; MARK PAINTER

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We have been speaking with many of you directly as states react differently to the arrival of the coronavirus in the United States. Stay-at-home orders and canceling of elective surgeries are spreading at the time of this writing. Many urology practices have already seen massive cancellations of in-office visits and surgical services. Others are preparing for changes that are coming.

As we hear from urologists and practices around the country, the primary concerns are centered around continued care for patients while maintaining the health and safety of both patients and staff. We have heard of many new and creative solutions for social distancing in the office setting for those patients requiring face-to-face care. It is impressive to see the talent and intelligence of the urology community.

We have also been impressed with the efforts of industry and the specialty organizations to help urologists stay up to date, push for legislative actions that allow for appropriate continuity of care, and in keeping the urology community at large in touch with one another. Keep thinking, keep planning, keep watching, and keep sharing. It takes a village, now more than ever.

ONLINE CODING RESOURCES

- **Urology associations:** the AUA (*www.auanet.org*), American Association of Clinical Urologists (*www.aacuweb.org*), and LUGPA (*www.lugpa.org*), as well as regional and state urology associations
- **Medical associations:** American Medical Association (*www.ama-assn.org*), American College of Surgeons (*www.facs.org*), Ambulatory Surgery Center Association (*www.ascaassociation.org*), and American College of Physicians (*www.acponline.org*)
- **Government:** Centers for Medicare & Medicaid Services (*www.cms.gov*), Centers for Disease Control and Prevention (*www.cdc.gov*)
- **Payer websites**
- **Other:** Physicians Reimbursement Systems Network (*www.prsnetwork.com*), American Telehealth Association (*www.americantelemed.org*).

For this article, we will focus on telemedicine and telehealth services. We will share what we know at this time, but know that changes are happening very quickly as payers, the government, patients, and practices react to this unprecedented crisis. There are several websites we encourage you to monitor to keep abreast of changes (see "Online coding resources").

CMS has clarified that it will not enforce the requirement that remote services be reported only for patients with whom the physician has a prior relationship, allowing you to provide new patient visits remotely (99201-99205).

In discussing the various options for remote services, we will first establish a vocabulary. Although many use these terms interchangeably, we are going to separate services into the following categories:

Telemedicine is the use of synchronous audio and visual communications to deliver health care at a distance.

Telehealth is the use of electronic and telecommunications technology to deliver asynchronous health care at a distance.

Several platforms available

There are a number of platforms that will allow you to interact with your patients using audio and visual communication. Prior to the COVID-19 outbreak, Medicare provided coverage to more than 100 CPT services as long as patients receiving care were located in a Medicare-approved facility located ("originating site") in a Health Professional Shortage Area (HPSA). The list of covered services included evaluation and management services, mental health, opioid addiction care, end-stage renal disease services, and other services deemed medically appropriate.

During this crisis, Medicare has relaxed several of the requirements for providing and billing for telemedicine services because during this public health emergency they believe patients should avoid unnecessary travel to physicians' offices, clinics, hospitals, or other health care facilities where they could risk their own or others' exposure to further illness. Here, we provide a summary of the changes and how they affect the urology office.

Medicare relaxed the originating site requirements and the HPSA requirements during the outbreak. Therefore, established patient outpatient visits 99212-99215 can be reported when provided to any patient regardless of the patient's location as long as the visit is conducted using a live audio and visual connection. Documentation for the visits has been relaxed and allowing level selection to be based on time spent that date related to the service or Medical Decision Making.

Payment for each code will be made at the same level as if the service were provided face to face in the outpatient setting. Billing requires you report the code for the visit using place of service 11 (the place-of-service code for office). A physician can provide these services from their home or other appropriate location. For purposes of billing, the location address for services should be the office number assigned to your Provider Transaction Access Number regardless of the actual location of the physician.

CMS has clarified that it will not enforce the requirement that remote services be reported only for patients with whom the physician has a prior relationship, allowing you to provide new patient visits remotely (99201-99205). Documen-

tation requirements are also relaxed, allowing level selection based on Medical Decision Making and time the same as established patient visits.

Medicare beneficiaries are generally liable for their deductible and coinsurance. However, to reduce the potential financial burden on Medicare beneficiaries, the Department of Health and Human Services Office of Inspector General stated they would provide flexibility for health care providers to reduce or waive cost-sharing for telehealth visits paid by federal health care programs. Should you choose to waive co-payments for these services, be careful to be consistent when offering this to patients. This option has been announced and may be expected by patients.

You may wish to develop a process for telemedicine visits that includes having the front desk speak with the patient with regard to billing and payment, having a medical assistant or nurse assist you to collect relevant history complaints and making sure the video and audio connection is of sufficient quality, and finally commencing the visit with the physician. The first two steps, up until the establishment of the connection, can be conducted with audio (telephone) only and can be accomplished prior to the visit similar to the flow established for an in-office visit.

Multiple options for obtaining patient forms/signatures

Forms typically required for new patients, including release forms, HIPAA policy explanation, and financial policies, can be obtained through patient portals. CMS has stated that forms can be signed after the visit has been provided and can be blanket coverage for an annual period, a verbal consent should be obtained and documented in the patient record.

As not all patients are well versed in the portal or use of the Internet, under the relaxation of HIPAA during the crisis, you should be able to use services like DocuSign to acquire patient signatures and other documents normally required when a new patient joins the practice. It also appears that you would be able to send forms via email and receive a scanned document (encrypted if possible) or returned via picture and messaging to the office; use this as a last resort.

Numerous applications can be used, such as What's App, that allow pictures to be sent in an encrypted format directly from a phone to a computer instead of using mobile phones in the office.

HIPAA rules have been relaxed as well. You are free to use FaceTime and Skype to conduct these visits without a Business Associate Agreement for CMS. You are required to take reasonable precautions such as avoiding the provision of these visits without others in the room who are not employed by your office. Further, we encourage you to respect your patients, explaining the purpose of others required in the room. If you have HIPAA-compliant tools, you should use them when possible.

In 2019, CMS expanded the ability to provide services remotely by adding new codes and extending coverage to new CPT codes for services provided using the telephone and other telecommunication platforms. The expanded coverage for these services prior to the COVID-19 outbreak required that the patient was an established patient, the patient initiated the encounter, the encounter was not related to an E/M visit provided in the last 7 days, and the visit did not result in instructions to have the patient come to the office at the next available appointment. The codes for these services and the descriptions are provided in a table available online at *www.urologytimes.com/covidtable*.

G2012 (Brief communication technology-based service, eg, virtual check-in) is intended for telephone calls initiated by a patient that are not related to or in follow-up of a recent E/M service for which the provider can manage the patient on the phone and the call does not lead to an in-person visit. It is important to document in the chart that

See **CODING AND COVID-19** page 41

Utilization review data: How do payers view your practice?

Improving your understanding of data beneficial in value-based care era

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The shift from fee for service to value-based care and reimbursement may be happening faster than some physicians like and slower than most payers would like. While urologic care is estimated to comprise only 2% of the "health care spend" in the U.S., it may not logically follow that urologists will delay or escape the consequences of oversight, scrutiny, and policies of government and commercial payers.

The increased burden of preauthorization faced by many physician practices is but one sign that payers are watching the dollars closely. Another trend is the availability of your practice and physician data in the public domain. In this article, I will review the concept of "utilization review" in the modern context and describe how you can gain insights into how payers and other stakeholders view your own practice.

Defining utilization review

Utilization review in health care dates to the 1970s and was defined by Merriam-Webster then as "a critical evaluation of health care services provided to patients that is made especially for the purpose of controlling costs and monitoring quality of care." The term evokes an image of a nurse, or an entire department, in a hospital poring over individual charts in the pursuit of reducing the cost of care in the hospital. Others may think of utilization review as a mechanism used by payers to systematically delay or deny care.

Many companies understand your utilization, payment, and prescribing data much more thoroughly than you might think.

In the modern context, utilization review is more likely to be conducted by examining large data sets looking for service patterns, outliers, or comparisons to a benchmark that can help lead to better "value."

One example familiar to many urologists is the American Board of Urology's collection of practice logs from diplomates during the maintenance of certification process. According to the ABU's website *(www.abu.org/lifelong-learning)*, "the practice logs allow the trustees to be certain that the Diplomate has a sufficient case load to maintain their skills. Most importantly we have the opportunity to provide feedback to the Diplomate."

Another example is the publication of utilization and payment data by physician in the Medicare program *(bit.ly/cmsutilizationdata)*. Medicare also publishes Part D prescriber data for individual physicians *(bit.ly/partdprescriberdata)*, and drug utilization and cost data. Commercial private payers have their own physician utilization data, though they do not usually publish it. Other companies collect pharmacy dispensing data, claims submission and remittance data, pharmaceutical sales data, and more—at the physician level. Many companies understand your utilization, payment, and prescribing data much more thoroughly than you might think.

How can you begin to understand your practice—as it is reflected in how much you "cost" those paying for the care—as well as these outside entities? The process begins with access to your claims data—something that almost all practice management systems allow in the application, with an inexpensive reporting module, by employing a third party with very basic database skills, or by using a commercial platform.

The next step that can be very helpful and save time is determining what question you would like to answer. For example, the data extracted for a review of procedures for stone surgery might be completely different than that needed for a comparison of physician in-office administration of injectable medications. By thinking through the purpose of your review and how you would act upon the results of that review, you can streamline the analysis, find your answers faster, and put that knowledge to work.

A common challenge in understanding utilization of health care services is comparing apples to apples. Building on the example of utilization of stone surgery, raw claims data are likely to show some physicians perform more surgery than others—perhaps by an order of magnitude (10 times) in a large practice. This information by itself is of limited use and needs to be calibrated to some reference common to the physicians being compared.

For example, the rate of stone surgery per unique patient with a diagnosis of a ureteral or renal stone might provide the necessary indexing to make a better comparison. The Quality Payment Program levels its comparisons of episode costs using risk adjustment. Commercial payers often index their utilization metrics simply to number of beneficiaries, and you can do the same.

Establish a benchmark

Another challenge in using utilization data is finding a definition of average, normal range, or outlier for comparison—a benchmark. Benchmarking in health care can be internal to an organization (such as comparing physicians in one practice) or external to an organization (such as comparing your urology practice to hundreds

See **UTILIZATION REVIEW** page 41

PRACTICE POINTERS

- In the modern context, utilization review is the examination of large data sets looking for service patterns, outliers, or comparisons to a benchmark that can help improve value.
- Examples of utilization review include the collection of diplomates' practice logs by the American Board of Urology and the publication of utilization and payment data by physician in the Medicare program.
- One challenge in using utilization data is finding a definition of average, normal range, or outlier for comparison—a benchmark.

CODING AND COVID-19

continued from page 39

the patient met these criteria, consented to the call, and understands that a bill will be sent to Medicare.

Code G2010 is a similar code, but when there is asynchronous (not real time) services provided ("store-and-forward"). During the COVID-19 outbreak, CMS has stated clearly that these services and six new service codes for Telephone only services 99441-99443 and 98966-98968 can be provided to new and established patients expanding the ability for continuity of care for your patients. The requirement for patient initiation of these visit types has also been relaxed during the crisis.

Finally, in regard to these services, if the patient requests a visit of this type but it is determined by the physician or advanced practice provider that a telemedicine visit is more appropriate given the patient complaints, the staff should communicate that the nature of the problem requires a telemedicine office visit. We recommend that scheduling staff be well trained to communicate the differences and circumstances.

Other codes are available that are intended for encounters performed using a patient portal or other HIPAA-compliant communication method. Check with your insurers to see which codes may be covered.

Coverage rules by payer

Medicare Advantage. Medicare Advantage plans are expected to allow for coverage under Medicare guidelines or establish guidelines that are less stringent. In 2019, Medicare relaxed requirements for Medicare Advantage plans to be restricted to Medicare rules. Therefore, Medicare Advantage plans can offer more services or establish rules that provide additional services than those allowed for Medicare. Check payer websites for guidance. Some of these payers may allow telephone visits for established patients to be reported with established patient visit codes (99212-99215). Billing for Medicare Advantage plans should require only use of the appropriate CPT code with place of service 11 and modifier –95.

We have been following the Medicare Advantage plans, and in general most allow for coverage under the relaxed rules and have gone beyond Medicare to allow additional services to be provided remotely. Many payers have indicated that the patient co-payment for remote services will be covered by the payer, meaning the group will be paid the full allowed amount by the insurer.

Medicaid. Medicaid programs are directed by the state. You will need to check with your state Medicaid program for coverage rules and billing for telemedicine and telehealth services. However, most states are relaxing requirements for remote services.

Commercial plans. Many commercial payer plans have policies that follow Medicare guidelines as they are published. With the emergency declaration, the larger payers have already released policies allowing for expanded coverage of both new and established office visits. Further, many of these payers are waiving patient responsibility for remote visits, promising to pay the full allowed amount for the encounters.

Some payers, in addition to using place of service 02, are requiring the use of modifier –95 (Synchronous Telemedicine Service Rendered Via a Real-Time Interactive Audio and Video Telecommunications System: Synchronous telemedicine service is defined as a real-time interaction between a physician or other qualified health care professional and a patient who is located at a distant site from the physician or other qualified health care professional. The totality of the communication of information exchanged between the physician or other qualified health care professional and the patient during the course of the synchronous telemedicine service must be of an amount and nature that would be sufficient to meet the key components and/or requirements of the same service when rendered via a face-to-face interaction. Modifier 95 may only be appended to the services listed in Appendix P. Appendix P is the list of CPT codes for services that are typically performed face-to-face, but may be rendered via a real-time [synchronous] interactive audio and video telecommunications system.)

Some payers may require place of service 11 and modifier –GQ, –GT to report these services.

Conclusion

Telehealth is a viable tool to solve the continuity-of-care issues faced during the coronavirus restrictions. Patients appear to be adapting to and even liking the new format. We would encourage you to adopt HIPAA-compliant practices as soon as possible but use the relaxed enforcement declaration to take care of your patients in need. We are projecting that after the outbreak remote visits in the form of telehealth and telemedicine will remain an option for patient care.

As you move past the initial scramble to reschedule and retool your practice, develop protocols and policies that will allow you to adopt telehealth and telemedicine technologies for patient care under new policies that will likely fall somewhere between where they were and where they are for the crisis. UT

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

UTILIZATION REVIEW

continued from page 40

of others across the country). Statistical methods used in benchmarking include comparisons to mean, median (the midpoint of data or 50th percentile), rank, or decile. Medicare's Quality Payment Program uses deciles in the Quality, Cost, and Promoting Interoperability categories to determine relative performance.

The median or 50th percentile is often a better point of comparison than the mean in health care data, which may not always follow a "normal" distribution. Available sources for external benchmarking of claims data include Medical Group Management Association survey data *(www.mgma.com/data)*, Medicare public use files mentioned earlier, the Quality Payment Program (limited at this point), and commercial platforms.

Perhaps the biggest challenge is once you understand your utilization data, you will need to decide what to do about it. Some decisions may be easy; if you have a large practice and a single outlier, your data and internal benchmarking may convince the outlier physician to examine and change their practice. Other decisions may be more difficult and require an external credible benchmark to support a crucial conversation. The larger that benchmark, the more closely you can understand the perspective of a large payer. The underlying premise for understanding and acting on your utilization data is the knowledge that this information is available, and being used, by the sources of revenue for your practice.

Bottom line: Your utilization data are widely available and understood by the federal government, commercial payers, and commercial data aggregators. Improving your literacy with your own data will position your practice to better face the challenges of value-based care and reimbursement. UT

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COVID-19 and market fluctuation: What you should do

Avoid making decisions motivated by emotion and fear

JEFF WITZ, CFP

Mr. Witz is educational program director at MEDIQUS Asset Advisors, Inc. in Chicago. He welcomes readers' questions and can be reached at 800-883-8555 or witz@mediqus.com.

Q: With fears about the coronavirus (COVID-19) causing the markets to fluctuate significantly, should I make any adjustments to my investment strategy?

A: The markets have certainly been a roller coaster lately. At the end of February, the Dow experienced its "first" largest single-day drop, down 1,191 points, then posted its largest single-day gain, at 1,293 points, a couple of days later. On March 10, the Dow beat its single-day loss record again by posting a jaw-dropping 2,021-point loss only to follow this up with a larger 2,997-point drop on March 16.

This volatility isn't unexpected when you have a stock market that was consistently setting new record highs come face to face with a potential global health threat. With a global pandemic causing countries to limit trade and social distancing limiting people's ability to purchase goods, it is likely that a highly volatile environment will remain for the short term.

As investors, it is critical not to overreact. You need to block out the surrounding noise and follow your investment strategy in the face of volatile markets. Actions based on emotion and fear can cause you to make mistakes that can negatively affect your long-term investment performance. In 2018, we wrote an article during another period of high volatility and provided some insights for investing in these environments. We would like to share those with you again.

Fight the impulse to sell your holdings if the markets are dropping. Selling after drops can make temporary losses permanent and difficult to recover. Sticking to your investment strategy, although it can be difficult emotionally, may be healthier for your portfolio. It is important to continue monitoring your investments but remember the long-term reasons the investment is in your portfolio. What role is it playing? If it is still a good fit, holding the investment may be the better long-term strategy.

Selling after market drops can make temporary losses permanent and difficult to recover.

Remember that you are investing for the long term. Markets have always fluctuated up and down, and during your lifetime, you're likely to experience several significant declines. Investors should ignore the noise and stay disciplined to the investment strategy they designed. The strategy was created specifically to avoid falling into these pitfalls.

Review your risk tolerance. Risk you took on years ago may no longer make sense given your current circumstances and stage of life.

Make sure your portfolio is well diversified. Volatile markets have a way of exposing improperly diversified portfolios.

Rebalance your portfolio. Market volatility can skew your allocation from its original target. Certain assets will be more affected by market swings and will move outside their target allocations. Rebalance your portfolio by selling positions that have become overweight in relation to the rest of your portfolio and move the proceeds to positions that have become underweight.

If you must trade during volatile markets, there are defensive steps you can take to protect your positions. Stop orders and stop-limit orders can help shield unrealized gains or limit potential losses on an existing position.

Consider adding defensive assets such as cash and cash equivalents, Treasury securities, and other U.S. government bonds. These can help stabilize a portfolio when stocks are slipping.

Q: If I want to take advantage of the down market, is there a preferred way to invest?

A: First, evaluate if you are in a financial position to invest more and proceed with caution. If you determine you are able to invest during a volatile environment, the best approach is to do so over a period of time. It is impossible to tell when the markets have hit their bottom. Don't try to guess and invest everything in one lump sum. If markets continue to decline, you could potentially lose a significant amount.

It is better to break up the investment into smaller increments. If you are wrong, you are not wrong with all the money you planned to invest. This strategy is called dollar-cost averaging. With a dollar-cost averaging strategy, it is best to select 1 day a week or 1 day a month to invest a smaller percentage of the total amount you planned to invest. By selecting a day and sticking to it, it will allow you to ignore the outside noise. If markets continue to decline, you are incrementally buying on the downslope and will be in a good position when markets recover. UT

FINANCIAL TIPS

- One way of coping with volatile markets is to rebalance your portfolio by selling positions that have become overweight in relation to the rest of your portfolio and move the proceeds to positions that have become underweight.
- Consider adding defensive assets such as cash and cash equivalents, Treasury securities, and other U.S. government bonds. These can help stabilize a portfolio when stocks are slipping.
- With a dollar-cost averaging strategy, investors break an investment up into smaller increments.

This activity is approved for *6.5 AMA PRA Category 1 Credits™*

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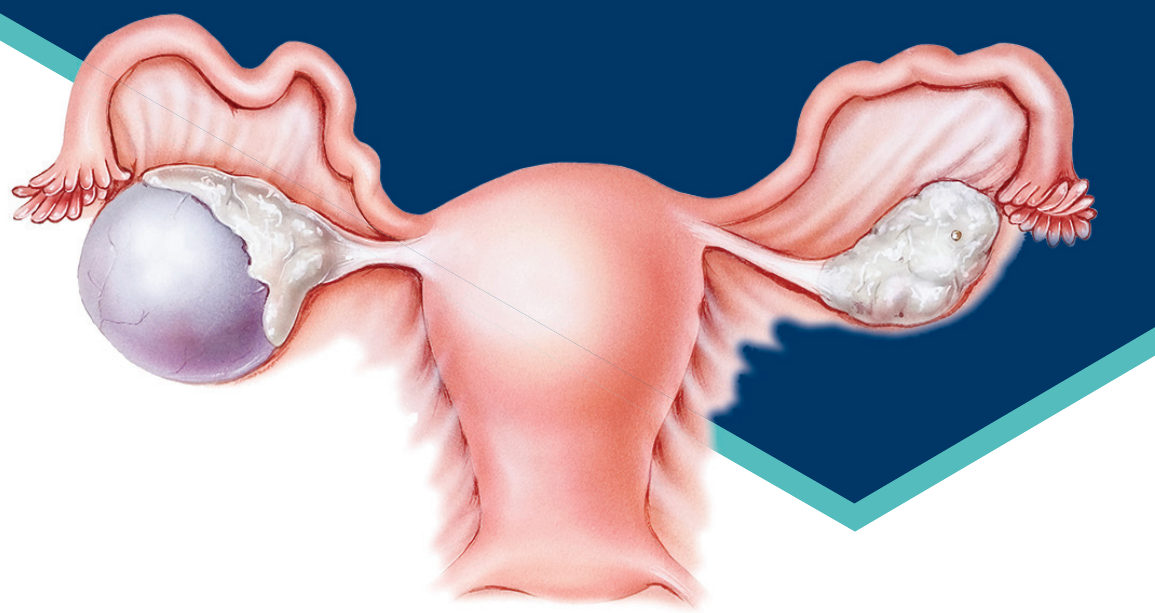

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Professor and Director, Division of Gynecologic Oncology
Creighton University School of Medicine
St. Joseph's Hospital and Medical Center
Medical Director, US Oncology Network – Gynecologic Oncology Research
Phoenix, AZ

Agenda Highlights

- Genetics, Genomics, and Precision Medicine: Efficient Integration of Powerful Tools in Ovarian Cancer
- Advances in Frontline Treatment Options for Patients With Ovarian Cancer
- MXF-Treatment Sequencing in a Patient With Newly Diagnosed Ovarian Cancer: Role of VEGF Inhibition
- Precision Medicine in Ovarian Cancer: When Understanding the Biology Cuts Deeper Than Surgery
- Impact of Biomarker Testing on Precision Medicine for Cervical Cancer
- Sequencing of Treatments for Endometrial Cancer: What Does the Science Say?

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Man sues over outcomes from microwave device

Urologist, proctor, device manufacturer all named in suit

ACACIA BRUSH PERKO, ESQ.

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

In the 1990s, the plaintiff, a male computer consultant in his mid-60s, started having mild lower urinary tract symptoms with urination one to three times nightly and minimal urinary bladder residual. His prostate was enlarged by ultrasound examination, but since his symptoms were not progressive, the defendant urologist advised him that surgical intervention was not warranted.

In early 2003, the defendant medical device manufacturer received FDA approval to distribute a device that used microwaves emitted from one portion of a catheter inserted into the patient's bladder to burn out portions of the prostate from the inside, a procedure designed to remove prostatic tissue obstructing the flow of urine without a surgical procedure.

After FDA approval, the defendant distributor approached the urologist and sold him one of the devices. The defendant proctor performed two microwave prostate removals with the urologist, and then issued a certificate on behalf of the manufacturer and distributor, indicating that the urologist had been fully trained and was competent to use the device without further supervision.

The urologist then performed an unsupervised microwave prostate removal on the plaintiff using the device. The plaintiff left the urologist's office in considerable pain and then experienced massive urinary incontinence, requiring the use of a diaper.

Two additional surgeries performed

Over the next 6 months, the urologist performed two other surgeries on the plaintiff, seeking to dilate strictures of the urethra.

The plaintiff alternated between frank urinary incontinence, requiring diapers, and bladder outlet obstruction, requiring self-catheterization.

The plaintiff then sought further opinions, and it was determined that his external urethral sphincter was damaged beyond repair and that he needed the implantation of a prosthetic urethral sphincter and resection of the portion of the urethra that appeared irreversibly strictured.

Claiming physical damages, the plaintiff sued the urologist for medical malpractice (negligent treatment), the manufacturer and distributor for product liability (design defect, negligence, fraud, failure to adhere to FDA requirements of approval), and the proctor for negligent training.

The urologist contended that, at all times, he was willing to undergo any training program that the manufacturer or distributor recommended and that he used the microwave device at all times exactly as instructed by the proctor and by the literature given to him.

The defense disputed the allegations.

The urologist contended that, at all times, he was willing to undergo any training program that the manufacturer or distributor recommended and that he used the microwave device at all times exactly as instructed by the proctor and by the literature given to him.

The manufacturer and distributor contended that the FDA did not explicitly require the exclusion of patients with prior strictures.

The manufacturer and distributor also contended that the Supremacy Clause precluded the claiming of any design defects in a lawsuit brought under state law when the FDA had approved the design and in fact precluded any lawsuits in tort under state law. The only recourse for the plaintiff, according to the manufacturer and distributor, was a complaint regarding noncompliance with FDA conditions of approval with the FDA having exclusive jurisdiction over any such litigation.

The manufacturer and distributor also claimed that the educational materials had been sent to and received by the urologist and that he was competent to proceed using the product without further supervision.

Settlements reached

Before trial, the urologist settled out for $200,000. A week before trial, the judge granted the remaining defendants' summary judgment, ruling that the Supremacy Clause, combined with FDA approval of the product and education program, pre-empted any and all state causes of action in tort.

The plaintiff appealed. Just before the reply brief was due, the manufacturer and distributor resolved the case for $195,000 with the plaintiff.

LEGAL PERSPECTIVE: The judge and jury have different functions. Judges decide matters of law, and juries decide questions of fact. The civil rules allow a party to move for summary judgment prior to trial, asking the judge to rule that there is no genuine issue of material fact and that they are entitled to judgment as a matter of law. If granted, a case will not proceed to trial.

Here, the remaining defendants, the manufacturer and distributor, moved for summary judgment, which was granted. The plaintiff appealed that decision to the higher court, asking the appellate court to reverse the trial court's decision. If successful, this would have resulted in a remand and trial.

Faced with the potential of protracted litigation, a likely sympathetic plaintiff, and the uncertainty of what a jury would do with the facts of the case, the manufacturer and distributor chose the safe bet of a settlement short of trial. UT

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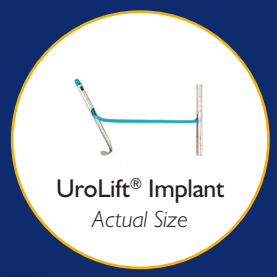

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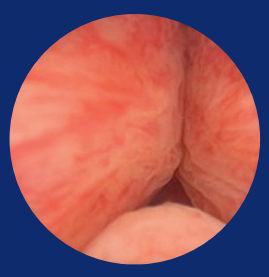
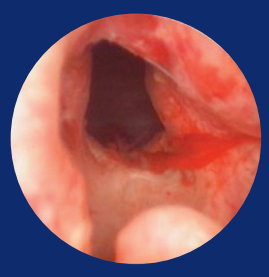


PRE-PROCEDURE



POST-PROCEDURE

To learn more about **My Story**, visit www.info.UroLift.com/Butler

Check out the data at **UroLift.com**

The UroLift System procedure is FDA-cleared for the treatment of symptoms due to urinary outflow obstruction secondary to BPH, including lateral and median lobe hyperplasia, in men 45 years of age or older. Results and patient experience may vary. Most common adverse events reported include hematuria, dysuria, micturition urgency, pelvic pain, and urge incontinence. Most symptoms were mild to moderate in severity and resolved within 2 to 4 weeks after the procedure. Consult the Instructions for Use (IFU) for more information.

*Dr. Butler is a paid consultant of NeoTract | Teleflex. Results may vary.
**No instances of new, sustained erectile or ejaculatory dysfunction in the FDA pivotal study.

1. Roehrborn, Can J Urol 2015; 2. L.I.F.T. IDE Study. Roehrborn. J Urology 2013; 3. AUA BPH Guidelines 2003, 2010, 2018; 4. Naspro, Eur Urol 2009; 5. Montorsi, J Urol 2008; McVary, J Sex Med 2016; 6. Shore Can J Urol 2014; 7. Roehrborn et al. Can J Urol 2017; 8. Eure et al J Endourol 2019

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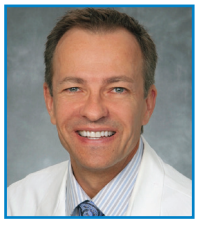

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Overview:

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Join leading experts as they debate and discuss the latest diagnostic, therapeutic, and supportive care strategies for patients with gynecologic cancers. The field has seen breakthroughs in treatment options in recent years, including the integration of targeted therapies and immunotherapeutics into clinical practice. Optimal implementation of surgery, chemotherapy, PARP inhibitors, antiangiogenesis agents, checkpoint blockade, as well as combination and other therapeutic strategies, will be analyzed and discussed both in frontline and recurrent disease settings. Case-based presentations will allow for vibrant discussion of the practical concerns of treating patients in the real world. Promising novel agents currently undergoing clinical trial evaluation will also be highlighted.

What You Will Learn:

- Understand the design, efficacy, and safety data of clinical trials investigating novel compounds and strategies for the management of gynecologic malignancies
- Apply the new findings and recently presented data in clinical context, and understand their therapeutic implications for the management of gynecologic malignancies
- Potentiate trial enrollment for eligible patients in order to evaluate new agents or strategies in the treatment of gynecologic malignancies

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Agenda

8:00 AM	Welcome, Introductions, and Presession Survey	Bradley J. Monk, MD, FACOG, FACS
OVARIAN CANCERS		
8:15 AM	Genetics, Genomics, and Precision Medicine: Efficient Integration of Powerful Tools in Ovarian Cancer	Michael Birrer, MD, PhD
8:40 AM	Advances in Frontline Treatment Options for Patients With Ovarian Cancer	Kathleen Moore, MD
9:05 AM	Mechanisms of Development and Strategies for Overcoming PARP Resistance	Gottfried Konecny, MD
9:30 AM	Incorporating Combination Therapy in an Evolving Treatment Landscape	Susana M. Campos, MD, MPH
9:55 AM	Break	
10:25 AM	Immunotherapeutic Updates in Ovarian Cancer	Ursula A. Matulonis, MD
10:50 AM	Future Directions: Where Are We Headed?	Maurie Markman, MD
11:15 AM	MXF-Treatment Sequencing in a Patient With Newly Diagnosed Ovarian Cancer: Role of VEGF Inhibition	Bradley J. Monk, MD, FACOG, FACS
11:40 AM	Cases and Q&A Session	Ursula A. Matulonis, MD
12:05 PM	Keynote Lecture—Precision Medicine in Ovarian Cancer: When Understanding the Biology Cuts Deeper Than Surgery	Robert L. Coleman, MD, FACOG, FACS
12:30 PM	Lunch	
CERVICAL CANCERS		
1:45 PM	Impact of Biomarker Testing on Precision Medicine for Cervical Cancer	Ritu Salani, MD
2:10 PM	What, When, Where: Sequencing Therapies for Cervical Cancer	Debra Richardson, MD, FACOG, FACS
2:35 PM	Future Directions: Emerging Therapies in Cervical Cancer	Bradley J. Monk, MD, FACOG, FACS
3:00 PM	Break	
ENDOMETRIAL CANCERS		
3:30 PM	Can Biomarker Testing Inform Treatment Decision Making in Endometrial Cancer?	Ramez Eskander, MD
3:55 PM	Sequencing of Treatments for Endometrial Cancer: What Does the Science Say?	Brian M. Slomovitz, MD
4:20 PM	Future Directions: Novel Agents and Treatment Strategies in Endometrial Cancer	Shannon N. Westin, MD, MPH
4:45 PM	Interactive Cases and Expert Discussion in Cervical and Endometrial Cancer	Robert L. Coleman, MD, FACOG, FACS
5:10 PM	Closing Remarks and Adjournment