American Urological Association

# AUA NEWS

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## INSIDE THIS ISSUE



# Telemedicine is Good for Patients and Providers in Sexual Medicine

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Telemedicine (TM) involves the use of electronic communication tools to obviate the need for an in-person clinic visit. Interestingly, this crossfire topic was chosen well before the pandemic arose and over the past few months TM has become an integral part of our practices.

While exact statistics on telehealth use vary regionally a 65% reduction in urology offices visits in April 2020 and a 35% reduction in May 2020 has been reported with a corresponding rise in use of electronic telehealth tools.

The crossfire question addressed by our panel was whether telemedicine is "good" for patients and providers. Drs. Nelson Bennett and Irwin Goldstein argued on the pro side and Drs. Arthur Burnett and Serge Carrier argued for the con viewpoint.

Dr. Goldstein made the analogy that telemedicine is as important a discovery as was sliced bread by Wonder Bread 99 years ago. He further stated that in time we will come to recognize TM as unassailably good as we do for apple pie, motherhood and toilet paper. He has used this tool for 4 years and finds it particularly helpful for prison inmates, hospital meetings and patients living out of state. He further stated that it is convenient, avoids the need for patient travel, full waiting rooms and fits into the busy patient schedules. The specific limitations of telemedicine he outlined were patients with cognitive challenges, the need for a physical examination, emergency cases and for research protocols. In summary, he believes use of TM is not a question of if you should or will use it but when.

Dr. Burnett arguing for the con side made many salient points. He cited several notable advantages including reaching underserviced populations and potentially a means of addressing workforce shortages but made the point of the lack of physician compensation for these patient interactions and that potential medical legal liability issues remain concerns.

He evaluated the critical questions of how well TM delivers patient care and whether providers and patients are satisfied with the TM experience. Internet health care delivery of sexual medicine is a rapidly growing commercial enterprise with hims® and Roman each reporting about 2 million visits to their websites monthly. Dr. Burnett pointed out that the AUA guidelines for erectile dysfunction (ED) specifically state that a physical examination for men should be done.[1] This cannot be done via TM assessment. The AUA guideline

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**AUA RESIDENTS & FELLOWS** *Committee News*

# Equity, Diversity and Inclusion in the Urology Workforce: The Time is Now

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As the world contends with the devastation of the COVID-19 pandemic and the U.S. is engulfed by high profile cases of racial injustice, renewed and pressing questions arise regarding the duty of physicians to uphold the principles of justice and equity. Many in urology have called for increasing the diversity of

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## Telemedicine and Sexual Medicine

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for testosterone management also states that a targeted physical examination should be performed.[2]

In support of his contention that TM and the lack of a physical examination may result in inferior patient care Dr. Burnett cited 2 AUA2020 abstracts (20-8081 and 20-766) which reported that up to 54% of men younger than 40 years of age have findings on examination that may be missed by TM assessments that routinely deviated from the AUA guidelines. Additionally, he supported his views with a recent publication by Mulhall et al that identified that comorbid conditions can often be found if a careful holistic evaluation of sexual dysfunction is performed.[3] With TM this cannot be done, and in summary he stated that TM does not provide a comprehensive evaluation, potentially leading to misdiagnosis and mismanagement.

Dr. Bennett made very compelling points in his presentation for the pro side. The first use of TM was in the United States in the 1950s. With the advent of the Internet in the 1980s an explosive expansion of use and technology has been witnessed. From a patient perspective TM results in lower costs, reduced travel, less exposure to sick patients in the waiting room, no concerns about childcare or eldercare while away and better health. He identified that the average clinic visit results in 121 minutes away time for patients compared to 16 minutes for a TM visit. The average TM interaction saves the patient $150.[4]

He showed other reports that demonstrated a range of savings and that TM represents an opportunity for providers as there exist few outlets at present using the technology. In 2018 the Physicians Foundation survey reported just 18% of MDs were using TM,[5] whereas their 2020 survey reported 48% were now using this approach,[6] indicating a broad upswing in its use and a clear recognition of its value. Reimbursement had previously been a major issue for TM but is now largely resolved with 49 states providing TM funding and parity reimbursement to physicians for care in most states.

A recent publication has shown that TM may be more profitable than an in-person visit for some clinics with recovery of capital costs in a few months for a typical busy sexual medicine practice.[7] In summary he stated that there are clear financial benefits to patients and physicians of TM. These benefits far outweigh the risks.

Dr. Carrier in support of the con side of the crossfire debate outlined the enormity of the sexual health online business, focusing on direct-to-consumer (DTC) ads and health care, that have grown into the many billions of dollars without sufficient regulatory oversight.[8] For direct-to-consumer TM Dr. Carrier reported that following a questionnaire completion by the patient a nurse or allied health care professional does a file review, but the physician's role may eventually be eliminated from this clinical activity completely.

**Dr. Goldstein made the analogy that telemedicine is as important a discovery as was sliced bread by Wonder Bread 99 years ago.**

He stated that the TM approach of the DTC companies is more focused on selling a treatment than on comprehensive evaluation of the patient, and the link between cardiovascular disease and erectile dysfunction may not be uncovered.[9] Furthermore, he expressed a concern about nonorganic ED being treated lifelong with drugs. He stated that TM without the ability to perform a physical exam is not in compliance with AUA guidelines. A recent online report from *Urology* identified in a population of 388 men younger than 40 years that comorbid conditions existed in many including 15% obesity, 20% diabetes or prediabetes, 54% dyslipidemia, 20% hypogonadal and 35% had a varicocele. These may be missed if a TM evaluation alone is done without an in-person visit.

In summary, Dr. Carrier believes it is sad that a questionnaire may replace a physician, significant comorbid conditions may be missed and the lack of direct interaction may fail to identify psychological distress in this population. TM may result in misdiagnosis and mismanagement in his view.

### Moderator Summary

The viewpoints expressed in this crossfire debate clearly identified the benefits and limitations of TM in sexual medicine. Particularly during this pandemic–where seeing a physician in person represents a potential risk particularly for the elderly or those with comorbid conditions, has an increased cost and requires travel time–in the context of limited clinic availability TM offers a viable option. The value of an in-person physician visit was not questioned by any of the panelists and all agreed that the ability to identify comorbid conditions and perform a physical examination is important.

TM has unique advantages for patients who are unable or unwilling to have an in-person visit and accept its limitations. The ability for urologists to service our patients with TM represents an important adjunctive approach to deliver quality health care to many.

In my view the emergence and recognition of TM during the pandemic by patients and providers will serve to expand its use and acceptance for sexual medicine concerns in the future. ◆


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## AUA Residents & Fellows Committee News

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our health care workforce to more closely represent demographics of the populations we serve.

The term "underrepresented in medicine" (URM) was coined to define racial and ethnic populations underrepresented in health care in comparison to the general population.[1] According to the 2019 AUA census data only 2% and 3.9% of practicing urologists and 3.1% and 5.7% of urology residents self-identified as Black and Latinx, respectively.[2,3] By contrast, Black and Latinx people represented 13.4% and 18.5% of the U.S. population, respectively, in 2019.[4] In the 2018 to 2019 academic year 7.1% and 6.2% of medical school matriculants and 4.3% and 7.6% of urology residency applicants identified as Black and Latinx, respectively.[5] The reasons for this low representation are often rooted in institutionalized barriers resulting in differential access to opportunity such as clinical, research and mentorship exposures. For example, fewer URM applicants shadow a urologist prior to their third year of medical school vs their nonURM peers (31% vs 67%).[6]

Whereas diversity may be measured quantitatively, inclusion is a cultural value of belonging set by leadership. In 2008 urology program directors were surveyed on preparedness for training a diverse residency cohort. Of those surveyed 5% and 2% identified as Black and Latinx, respectively, and 75% noted no diversity training for program directors or residents, and for the recruitment of trainees and faculty.[7] Although structured mentorship has been shown to facilitate professional thriving and foster inclusion, URM trainees are more likely to lack this mentorship.[8] Additionally, only 11% of URM urologists stay in academics compared to 24% of their nonURM peers.[9] There is a well-documented phenomenon of URM physicians leaving academics at disproportionate rates, reporting barriers to career advancement, unequal salary, lack of departmental leadership support and discrimination.[10] Institutions without defined investments, policies and structures promoting inclusion are at risk of high levels of attrition of URM physicians.[11]

Increasing minority representation in urology is of measurable benefit as diverse teams have been shown to outperform nondiverse groups, focus more on facts and be more innovative.[12] Notably, URM physicians provide increased access to care for minority populations, better communication between providers and patients, and improved patient decision-making.[13] Moreover, researcher demographics have the potential to impact research outcomes by ingroup vs outgroup effects, and stereotype and implicit bias effects. Therefore, diversity in the physician-scientist population may increase diversity and engagement among research participants.[14]

Urology has successfully increased female representation from 1.2% of practicing urologists in 1995 to 9.9% today.[15] It is time to see similar initiative taken for URM urologists. We urge the urology community to advocate by assessing the recruitment policies of our training programs and governing bodies, diversifying the pool of qualified medical school applicants, supporting URM students so they thrive during their medical education, ensuring early exposure to urology, adequately preparing them for the application so they successfully match and promoting inclusion to ensure retention in academics. We look forward to learning of the strategies our professional community employs in the upcoming Gold Journal edition devoted to disparities in urology. ◆


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# Penile Length Loss during Nesbit Type Surgery: A Prospective Study




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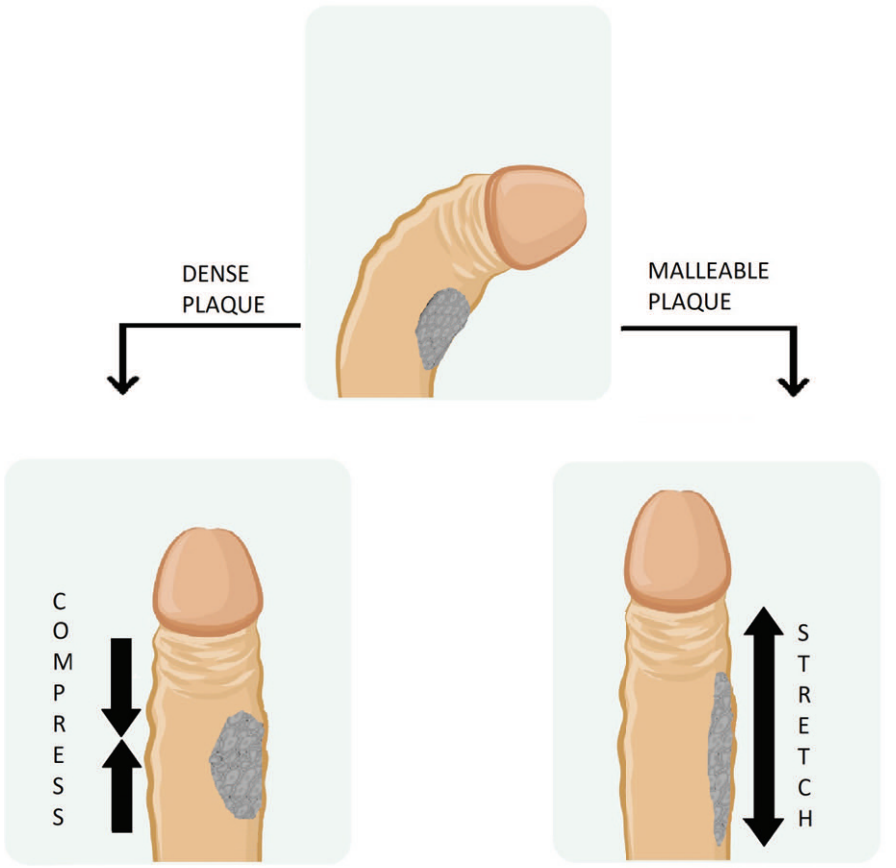


**Figure 2.** Theoretical model of how flexibility of Peyronie's plaque influences PLL. A malleable plaque stretches throughout surgery thus PLL is minimal. Conversely to straighten a penis with dense plaque longer side is plicated and compressed down resulting in a greater PLL.

## Introduction

In 1965 Dr. Reed Nesbit described a novel surgical technique to correct penile curvature by excising elliptical wedges of tunica albuginea.[1] Modifications of this initial surgical technique have resulted in Nesbit type surgery that include plication, incisional corporoplasty and excisional corporoplasty. Common among all Nesbit type surgeries is the necessity to shorten the convex side of penis to straighten the curved erection.

Penile shortening occurs in many patients as part of the Peyronie's disease plaque formation. Patient focused research has shown a common concern preoperatively for the potential of further penile length loss (PLL) associated with surgical correction. Counseling patients preoperatively needs to include the expected PLL. Patient information leaflets are widely used to aid the decision making and consent process. The AUA Peyronie's disease guideline does not comment on expected PLL. The British Association of Urological Surgeons (BAUS) information leaflet states 10 mm length loss per 15 degree curvature correction. In our experience this predicted PLL seems particularly excessive.

The aim of this study was to determine the PLL attributable to surgical correction and whether there were any predictive factors of PLL.

## Methods

A single center, 3-year prospective cohort study was undertaken of all patients undergoing penile curvature Nesbit type procedures. Patients who required grafts were excluded. Stretched penile length (mm) was recorded preoperatively by extending the flaccid penis to its natural maximum length. After reducing the prepubic fat pad by pushing the fat toward the pubis the penile length was measured from the base of penis at the pubopenile junction to the tip of the glans along the dorsal surface.[2] Surgery was performed without a tourniquet using a prostaglandin induced erection. Biplanar penile curvature was measured using a goniometer at the start of surgery. Postoperative penile length and penile curvature were measured prior to detumescence with phenyl-ephedrine.

Variables recorded included preoperative and postoperative curvature, precorrection and postcorrection penile length, mode of correction and number of incisions/plications. Data were analyzed via scatterplot with line of best fit to determine penile length loss per degree of curvature correction. Multivariate regression analysis was used to determine causal relationships between length loss and preoperative factors. Patients were reviewed in an outpatient setting 3 months postoperatively.

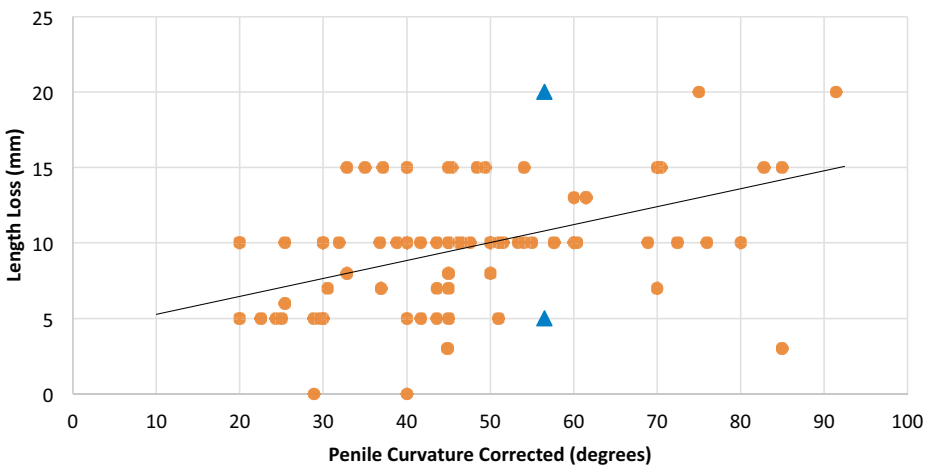


**Figure 1.** Penile length loss (mm) following Nesbit-type surgery vs curvature corrected (degrees). Blue triangle identifies patients undergoing the same degree of curvature correction (56 degrees) who experience a great difference in PLL (5 mm and 20 mm).

## Results

A total of 101 patients underwent Nesbit type surgery and all were included in the analysis. Mean preoperative curvature measured 46.4 degrees (IQR 19.9, range 20–91.6). Mean postoperative curvature was 1.7 degrees (range 0–5).

Mean preoperative penile length was 161 mm (IQR 1, range 135–190). Mean postoperative penile length was 152 mm (IQR 15, range 120–180) resulting in a mean penile length loss of 9 mm (IQR 3, range 0–20). Two patients had no objective penile length loss despite undergoing a 29 degree and 40 degree penile curvature correction. In all, 82.1% (83) of patients experienced 1 to 10 mm of PLL and 15.8% (16) experienced 11 to 20 mm PLL. From scatterplot line of best fit mean length loss per 15 degree of curvature correction was 3.6 mm (fig. 1). Multivariate regression analysis revealed that the method of surgical correction implemented (ie ellipses, plication or combination approach) was not a significant factor affecting length loss.

## Conclusion

We report that PLL as a result of Nesbit type surgery is significantly less than previous literature suggests. All patients in this study experienced less PLL than the BAUS patient information leaflet counsels

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## Penile Length Loss and Nesbit Type Surgery

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patients to expect. Despite the frequency of Nesbit type surgery there is a paucity of outcome data which clearly document PLL. Cantoro et al reported that 22.5% of patients who had undergone penile plication surgery experienced PLL between 15 and 30 mm, but the authors did not comment on PLL less than 15 mm.[3] In our cohort 15.8% experienced a PLL of 11 to 20 mm. As the technique of penile length measurement was not included in their methodology limited comparisons can be made. Lopes et al reported on the outcomes of Nesbit type surgery (Yachia's technique) for 117 patients in which almost all patients reported PLL.[4] For Lopes' included patient self-reported subjective measurements of PLL the mean PLL was 18 mm (range 0–50). This PLL is greater than our experience. However, it must be taken into consideration that we are comparing a subjective patient reported measurement to an objective measurement taken by clinicians.

Despite the severity of PLL being greater in previously published literature it is important to counsel patients that the satisfaction postoperatively remains high and that it is unusual for the PLL to have a negative impact on overall sexual satisfaction.

Our data show a large variation in PLL experienced among patients with the same degree of penile curvature corrected. This is best demonstrated by the 2 blue triangle highlighted data points in figure 1. Both patients underwent a 56 degree penile correction with 1 patient experiencing only a 5 mm PLL and the second patient experiencing 20 mm PLL. Similarly, 10 mm of PLL is seen in a patient with a 20 degree penile curve correction as well as a patient who had an 80 degree curve correction. We propose that the variability in PLL and degree of curvature correction are caused by variable plaque densities that allow for variable elastic remodelling during correction. As demonstrated in figure 2 if the tunica of the shorter penile side is flexible and has the potential to stretch when Nesbit surgery is performed on the longer, contralateral side then the length loss will be minimal. Conversely if the plaque and the surrounding tunica are dense and will not stretch, then the longer penile side has to be plicated and shortened around a fixed plaque and thus penile length loss will be significantly greater. This highlights the importance of examining the patients with a PGE-1 induced erection as part of the preoperative period to assess for flexibility of the plaque and not to rely on patient photographs.

Further analysis is required to ascertain a theoretical model predictor of penile length loss to enable more patient specific counseling before penile curvature surgery.

*AUA 2020 Virtual Science Best Poster winner.* ◆


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## 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%)

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# START EARLY WITH ERLEADA®

## TO PUSH BACK ON PROGRESSION

**mCSPC**

In the TITAN study*†:
**33%** reduction in the risk of death[1]
(ERLEADA® + ADT vs placebo + ADT; median overall survival was not estimable in either arm; HR=0.67; 95% CI: 0.51, 0.89; *P*=0.0053)

**nmCRPC**

In the SPARTAN study‡§:
**2-YEAR** improvement in median MFS[1]
(ERLEADA® + ADT vs placebo + ADT; 40.5 months vs 16.2 months; HR=0.28; 95% CI: 0.23, 0.35; *P*<0.0001)

**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.

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ADT = androgen deprivation therapy; AR = androgen receptor; CI = confidence interval; CT = computed tomography; GnRH = gonadotropin-releasing hormone; HR = hazard ratio; mCSPC = metastatic castration-sensitive prostate cancer; MFS = metastasis-free survival; nmCRPC = non-metastatic castration-resistant prostate cancer; PSA = prostate-specific antigen; rPFS = radiographic progression-free survival; SPARTAN = Selective Prostate Androgen Receptor Targeting with ARN-509; TITAN = Targeted Investigational Treatment Analysis of Novel Antiandrogen.

*__Study Design:__ TITAN was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of patients with mCSPC (N=1052). Patients had newly diagnosed mCSPC or relapsed metastatic disease after an initial diagnosis of localized disease. 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 or placebo orally once daily. All patients in the TITAN trial received a concomitant GnRH analog or had a prior bilateral orchiectomy. The dual primary endpoints were overall survival and rPFS.[1,2]

†All patients who enrolled in the TITAN study started ADT for mCSPC ≤6 months prior to randomization.[2]

‡__Study Design:__ SPARTAN was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of patients with nmCRPC (N=1207). Patients had a PSA doubling time ≤10 months and serum testosterone levels <50 ng/dL. All patients enrolled were confirmed to be non-metastatic by blinded central imaging review. 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. Patients were randomized 2:1 to receive ERLEADA® 240 mg orally once daily or placebo orally once daily. All patients in the SPARTAN trial received a concomitant GnRH analog or had a bilateral orchiectomy. The primary endpoint was metastasis-free survival (MFS), defined as the time from randomization to the time of first evidence of blinded independent central review-confirmed distant metastasis, defined as new bone or soft tissue lesions or enlarged lymph nodes above the iliac bifurcation, or death due to any cause, whichever occurred first. Secondary endpoints were time to metastasis, progression-free survival, time to symptomatic progression, overall survival, and time to initiation of cytotoxic chemotherapy.[1,3]

§In the SPARTAN study, conventional imaging (technetium-99m bone scans and CT scans) was used to confirm that patients were non-metastatic at screening for inclusion. Patients with pelvic lymph nodes <2 cm in short axis (N1) located below the iliac bifurcation at screening were allowed in the study. All patients in SPARTAN had a PSA doubling time ≤10 months at study entry.[1,3]

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

**References: 1.** ERLEADA® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Chi KN, Agarwal N, Bjartell A, et al; for the TITAN Investigators. Apalutamide for metastatic, castration-sensitive prostate cancer. *N Engl J Med.* 2019;381(1):13-24. **3.** Smith MR, Saad F, Chowdhury S, et al; for the SPARTAN Investigators. Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med.* 2018;378(15):1408-1418.

Erleada® (apalutamide) 60 mg tablets

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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 |



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

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

[1] Includes fatigue and asthenia

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

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

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

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

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

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

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

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

[1] Does not reflect fasting values

Rash

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

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

Hypothyroidism

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

### Post-Marketing Experience

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

*Respiratory, Thoracic and Mediastinal Disorders: interstitial lung disease*

## 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]*.
- Instruct patients who have difficulty swallowing tablets whole to mix the recommended dose of ERLEADA tablets with applesauce. Do not crush tablets *[see Dosage and Administration (2.3) 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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Gurabo, PR 00778

Manufactured for:
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# Erectile Function after HoLEP: Results from a Prospective Trial



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Surgical treatments for lower urinary tract symptoms (LUTS) due to benign prostatic enlargement (BPE) have been variably associated with postoperative erectile dysfunction (ED) with comparable outcomes between conventional transurethral resection of the prostate (TURP) and laser techniques such as holmium laser enucleation of the prostate (HoLEP).[1] The pathophysiology of postoperative ED remains poorly understood for patients surgically treated for LUTS/BPE, although the psychological impact of surgery along with transient irritative urinary symptoms occurring after the treatment could play a significant role.[2] Moreover, it has previously been shown that the postoperative improvement of LUTS may lead to an amelioration of erectile function (EF) for patients with severe LUTS associated with ED at baseline.[3,4] As such, we could expect a progressive recovery and improvement of EF over time after surgery. Therefore, in this study we investigated the time dependent changes for EF after HoLEP for LUTS/BPE.

The findings of a prospective observational study (the ExpHo trial, NCT03583034) including patients submitted to HoLEP by a single highly experienced surgeon with more than 1,000 procedures completed at a single academic center were analyzed. All patients completed the International Index of Erectile Function (IIEF) and the International Prostatic Symptoms Score (IPSS) at baseline before surgery. Nonsexually active patients were excluded. Throughout followup patients have been reassessed at 1 week and at 1, 3, 6 and 12 months. We defined postoperative EF recovery as an IIEF-EF score equal to or higher than baseline values. We used Kaplan-Meier analyses to estimate the probability of EF recovery over time. Cox regression analysis tested potential predictors of EF recovery.

Complete data were available for 72 sexually active patients. At baseline median (IQR) age was 66 (62–73) years. Most patients had severe LUTS with a prostate volume greater than 80 cc (median IPSS 20, prostate volume 90 cc). Overall, 64% of patients did complain of ED even before surgery with 54% reporting severe ED according to the IIEF-EF domain score. After surgery we observed a significant decrease of mean IIEF-EF score at 1 month followup compared to baseline (18.8 vs 13.5, p=0.0008) with a subsequent improvement at 3 months (IIEF-EF 17.1) and 6 months (IIEF-EF 21.4) assessments. Interestingly, 47.2% of patients reported EF improvement at last followup compared to baseline. According to Kaplan-Meier analysis the estimated probability of EF recovery after surgery was 42% (95% CI 30–55), 60% (95% CI 48–73) and 80% (95% CI 65–92) at 1 month, 3 months and 6 months after surgery, respectively. At Cox regression analysis preoperative clinical factors including age, body mass index, comorbidities, prostate volume and baseline IIEF and IPSS, as well as intraoperative variables (ie duration of surgery, total energy delivered, intraoperative complications) were not associated with the probability of EF recovery over time.

Overall, these data confirm a time dependent recovery of EF after HoLEP. The majority of patients experience a significant EF decrease in the early postoperative period. However, of those most are likely to recover their baseline EF status after 6 months. It is reasonable to believe that more than 90% of patients could eventually recover EF at longer followup assessment. Of interest, we also confirmed previous findings reporting that a non-negligible rate of patients may even improve their baseline EF after surgical treatment.[3,4] This is likely to be associated with LUTS relief and overall quality of life improvement, although we were not able to identify predictors of postoperative EF improvement, probably because of the small number of patients included in these analyses.

At the time this article was written about 200 patients were recruited in the ExpHo trial at our center, and we expect to provide updated data with a longer followup during the next year. Overall, we believe that these findings may help physicians in counseling their patients in terms of EF outcomes after HoLEP during the management workup.

*AUA 2020 Virtual Science Best Poster winner.* ◆

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# How Well Do Patients Recall Their Urinary Symptoms?

**Kathryn E. Flynn, PhD**
**The LURN Study Group**
Milwaukee, Wisconsin

Providers rely on the accuracy of patient self-reported lower urinary tract symptoms (LUTS) for clinical decision making, to guide treatment options and to gauge treatment responsiveness. When they use a questionnaire or patient reported outcome measure to ask patients about their LUTS the questions typically include a specific recall period (eg "In the past 30 days…"). But how well are patients able to accurately report on their experience during a week or a month? Are certain patients more likely to exaggerate or overreport their symptoms?

The Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN) conducted the LURN Recall Study to inform the recall period for the LURN Comprehensive Assessment of Self-reported Urinary Symptoms (CASUS)[1] and other LURN patient reported outcome measures for women and men.[2,3] At the 2019 AUA annual meeting we reported on the main results of the Recall Study, which is that compared to averaged daily reports 7-day and 30-day recalled reports of LUTS were generally unbiased but recall bias varied by item.[4] The LURN Recall Study also sought to evaluate whether recall bias was related to participant demographic and psychosocial characteristics. To our knowledge no previous studies had examined whether an individual's personal characteristics were related to accuracy of LUTS recall for women and men across a variety of LUTS.

We presented our examination of whether age, symptom bother, anxiety and other characteristics were associated with 30-day recall of LUTS at the AUA 2020 Virtual Symposium, and the results have now been published in *Neurourology and Urodynamics*.[5] Participants were recruited from 6 U.S. tertiary care sites and included 127 women with a mean age of 58 years and 127 men with a mean age of 62 years. They completed daily assessments for 30 days and a 30-day recall assessment at the end of the study month.

We found that many of the items we tested exhibited underreporting or overreporting (recall bias) for at least 25% of participants (see Appendix). These included items on stress incontinence, urgency incontinence, nocturia, urgency, slow/weak stream, incomplete emptying and postmicturition dribble. Items on daytime frequency and other/unknown incontinence

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## Patient Recall of Urinary Symptoms

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did not have notable recall bias, and while there was systematic overreporting of incomplete emptying it was not associated with participant characteristics in a noteworthy way. However, recall bias was associated with patient demographic and psychosocial characteristics for 6 symptoms. Older age and lower anxiety were associated with underreporting urgency incontinence among women. For stress incontinence (incontinence with laughing, sneezing or coughing) higher negative effect and lower anxiety were associated with underreporting among women. For other LUTS patient characteristics were associated with overreporting. Men overreported nocturia compared to women. Multiple characteristics were associated with overreporting urgency including lower anxiety, lower depression, higher symptom variability and lower symptom bother (among women only). Lower symptom bother was also associated with overreporting of slow/weak stream, and lower symptom variability was associated with overreporting of postmicturition dribble.

A limitation of the LURN Recall Study is the sample of generally well-educated, English speaking, specialty care seeking participants, which does not represent all people with LUTS. Nevertheless, the sample was sufficiently diverse with respect to sex, age and symptoms with minimal dropout during the study.

Overall, our findings suggest that there are few reliable cues for detecting which patients are more likely to report inaccurately. Furthermore, some cues (eg less bother and lower anxiety) were related to recall bias in an unexpected direction. Therefore, providers should exercise caution when making judgments about the accuracy of patient symptom recall based on overt patient characteristics. These results may help researchers and clinicians assess the likelihood and direction of recall bias for 30-day recall settings, and they may have implications for other urological conditions that rely on patient self-reporting.

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**Appendix.** Patient characteristics associated with recall bias

| Symptom | Recall Bias* | Associated Characteristic(s) |
|---|---|---|
| Stress Incontinence | Underreporting | Higher negative affect (women)<br>Lower anxiety (women) |
| Urgency Incontinence | Underreporting | Older age (women)<br>Lower anxiety (women) |
| Other Incontinence | None | n/a |
| Daytime Frequency | None | n/a |
| Nocturia | Overreporting | Male sex |
| Urgency | Overreporting | Lower symptom bother (women)<br>Lower anxiety<br>Lower depression<br>Higher symptom variability |
| Slow/weak Stream | Overreporting | Lower symptom bother |
| Incomplete Emptying | Overreporting | None |
| Post-micturition Dribble | Overreporting | Lower symptom variability |

*Systematic over- or underreporting where at least 25% of participants had bias of at least 10%

This study was supported by the National Institute of Diabetes & Digestive & Kidney Diseases through cooperative agreements (grants DK097780, DK097772, DK097779, DK099932, DK100011, DK100017, DK099879).

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# Intramuscular Injection of Ketorolac at Ureteral Stent Removal Decreases Pain Related Return Visits



**Brett A. Johnson, MD** **Jodi Antonelli, MD** **Margaret Pearle, MD, PhD**

Dallas, Texas

Ureteroscopy (URS) for the treatment of renal and ureteral calculi can be associated with significant patient perceived morbidity largely as a result of symptoms associated with stents. Indeed, stent related pain is the focus of an ongoing multicenter research initiative funded by the National Institutes of Health and the National Institute of Diabetes and Digestive and Kidney Diseases (https://usdrn.org/stents). While most patients receive preoperative counseling about the possibility of stent discomfort few patients are prepared for acute renal colic following stent removal and fear they are passing another stone.

The etiology of renal colic after stent removal is not well understood. It has been postulated to be a consequence of ureteral spasm or edema causing transient upper tract obstruction. In a recent study of 571 patients who underwent office stent removal 32% developed severe pain after stent removal and 9% returned to the emergency department (ED).[1] Any measures that can potentially reduce the

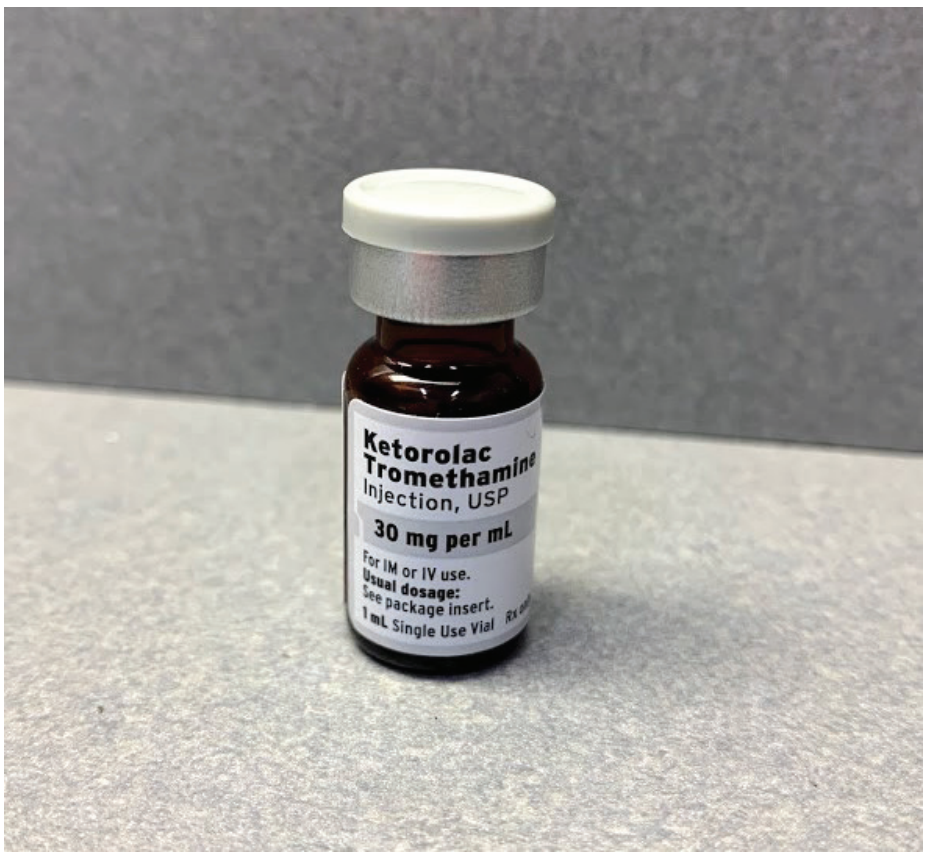


**Figure.** Ketorolac tromethamine.

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## Decreasing Pain Related Return Visits with Ketorolac

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occurrence of poststent removal renal colic should reduce cost, unnecessary imaging and need for pain medication.

In the absence of infection the obstruction associated with ureteral spasm is generally transient, typically resolving in a few hours to up to 24 hours. However, more persistent pain can indicate a more serious problem such as obstruction from an untreated stone fragment or stricture, pyelonephritis or renal hematoma. As such, the clinician should further pursue other etiologies for the pain.

Ketorolac tromethamine (see figure) is a safe and commonly used nonsteroidal antiinflammatory (NSAID) medication for acute renal colic.[2,3] Although there is concern for renal failure and bleeding risk with the administration of NSAIDs, particularly in high risk patients, studies have demonstrated that the risk of renal failure when used for less than 5 days and bleeding risk with ketorolac are very low.[4] Furthermore, ketorolac is not habit forming like its opioid based counterparts. While an oral form of ketorolac exists it is only approved for use after an intramuscular or intravascular loading dose. We sought to investigate the role of routine administration of intramuscular ketorolac at the time of ureteral stent removal to mitigate the transient renal colic following stent removal.

We performed a prospective, randomized, double blind, placebo controlled trial assessing the efficacy of intramuscular ketorolac administered at the time of ambulatory stent removal in reducing the incidence of poststent removal renal colic. Patients randomized to the treatment arm were given 30 mg intramuscular injection of ketorolac immediately before removal of the ureteral stent in the ambulatory urology setting. Patients in the control arm were given a 1 ml intramuscular injection of 0.9% normal saline. The patient, surgeon and nurse administering the injection were blinded to the contents of the syringe.

A total of 124 patients were randomized to a control group (62) or a treatment group (62). There were no significant adverse reactions or complaints about the injection. Pain endpoints were similar between groups. However, the primary endpoint of unplanned pain related encounters (ED or office visit) was significantly lower in the ketorolac group (1 ED visit) compared to the control group (8 patients required an urgent visit including 2 ambulatory urology visits and 6 ED visits, 1 of which required hospital admission). Overall, we determined that 9.1 ketorolac injections are needed to prevent 1 unplanned pain related encounter.

We concluded from this study that it is possible to mitigate poststent removal renal colic with a prophylactic intramuscular injection of ketorolac. While we did not see a reduction in overall subjective pain measures at 24 hours it is likely that the pain had resolved by then as most reported episodes of renal colic significant enough to require an urgent ambulatory or ED visit occurred within the first 12 hours after stent removal. As the goal after any surgical procedure is to reduce the need for urgent and unplanned medical attention this is especially true in the era of Covid-19. We were able to reduce the need for urgent office or ED visits after stent removal eightfold with minimal risk for eligible patients.

Although administration of ketorolac before stent removal does not eliminate subjective poststent removal pain, it does reduce the likelihood of severe renal colic requiring ED or office visits. Consequently, adoption of this prophylactic intervention may improve patient outcomes.

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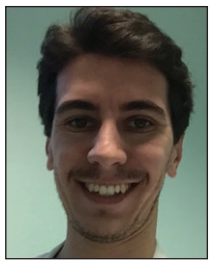
# The Learning Curve in Robot-Assisted Kidney Transplantation



**Andrea Gallioli, MD** **Angelo Territo, MD** **Alberto Breda, MD**

Barcelona, Spain

Open kidney transplantation is considered the best renal replacement treatment. In the second half of last century the impact of this surgical technique was dramatic. The first successful cadaveric kidney transplantation earned the Nobel Prize for Medicine in 1990 to Dr. Joseph Murray, the only Nobel Prize for Medicine involving a surgical procedure in the last 70 years. Nonetheless, the technological improvements that characterized the last 30 years have led to the introduction of minimally invasive kidney transplant.

Robot-assisted kidney transplantation (RAKT) has been recently reported in Europe. A European Association of Urology (EAU) Robotic Urology Section (ERUS RAKT) Working Group was constituted to draw together early European experiences at the highest volume centers using this minimally invasive technique. In 2018 the results provided by the 8 centers of the ERUS RAKT Working Group demonstrated the safety and feasibility of the technique in 120 patients.[1]

A potential limitation of RAKT is represented by the learning curve as the procedure requires the vascular skills to be translated in the robotic approach. On the other hand the use of the robot might improve the accuracy of the anastomoses and shorten the learning curve in robotic surgeons. For this reason, a study coordinated by the pilot center (Fundació Puigvert, Barcelona) was designed to assess the learning curve of RAKT. All consecutive RAKTs performed in the 5 highest volume centers of the ERUS RAKT Group (ie Fundació Puigvert, Hospital Clinic [Barcelona], Careggi Hospital [Florence], Ghent University Hospital [Ghent] and Bakirkoy Research Hospital [Istanbul]) were reviewed.

Shewhart control charts were used to analyze if the process was in control taking as referral values the cases reported by Breda et al with a rewarming time less than 48 minutes (+2SD=alert line, +3SD=alarm line).[1] The rewarming time is critical as it represents the time between the peritoneal insertion of the graft in the abdominal cavity and the start of kidney reperfusion. Cumulative summation graphs were generated to assess the learning curve according to surgical timings and renal graft function (glomerular filtration rate) at days 7 and 30 and at 1 year. Linear regressions were performed to compare the learning curves of each surgeon.

Our results demonstrated that the vascular anastomoses times were generally under control. In fact, the arterial anastomosis time was below the alarm/alert line in 93.3% and 88.9% of RAKTs, respectively, while venous anastomosis time was

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## Robot-Assisted Kidney Transplantation

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below the alarm/alert line in 88.9% and 73.9%, respectively. Moreover, the ureteroneocystostomy time was below +2 and +3SD in 87.9% and 90.2% of cases, respectively.

Conversely, the rewarming time was below the alert line in only 46% cases. Accordingly, the time spent during rewarming time without performing the vascular anastomoses exceeded +3SD in 24.7% of procedures and +2SD in 37.1%. Cumulative summation graphs showed that the learning curve for arterial anastomosis required up to 35 (mean 16) cases. A similar conclusion was reached for venous anastomosis, which may need more than 40 procedures (mean 24). The plateau in the ureteroneocystostomy curve was reached within 30 RAKTs in 4 of 5 centers (mean 17). The plateau for rewarming time was reached at a mean of 35 cases. Interestingly, the curves for nonanastomotic time during rewarming time resemble those for rewarming time. Complications and delayed graft function rates decreased significantly and reached a plateau after the first 20 cases. On the linear regression model all the anastomotic times were comparable. The slopes in respect of nonanastomotic time during rewarming time were slightly different (p=0.0006) as was also true for rewarming time itself (p=0.007).

We concluded that a minimum of 35 cases is necessary to reach reproducibility in terms of anastomosis time, rewarming time and functional results. Therefore, the study demonstrated a short learning curve to achieve optimal results among expert surgeons. It also underlined the importance of the synergic work between the robotic surgeon and the bedside assistant. Actually, the teamwork influences the rewarming time as the anastomotic time. Consequently, the initial steps of the technique should be taken by a dedicated team under proctorship.

The definitive results of the study were published in *European Urology*[2] while the abstract was accepted at the AUA Virtual Meeting 2020 and was awarded with the Best Poster Prize. The abstract was also awarded by the EAU Section of Transplantation Urology with the René Küss Prize 2020 for the best abstract of the section. The authors would like to thank all collaborators of the Group who helped to shed light on a crucial point of this promising surgical technique.

*AUA 2020 Virtual Science Best Poster winner.* ◆


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# AUA Live Panel Discusses Management of Testosterone Therapy Complications

**Amy Guise, MD**
Madison, Wisconsin

Since the start of the century there has been an exponential rise in testosterone replacement therapy prescribing. The diagnosis and management of hypogonadism continues to constitute a significant portion of many urologists' practice. The virtual format for the 2020 AUA Live allowed the panel (fig. 1) to have an interactive discussion about the management of the potential complications of polycythemia, gynecomastia, prostate concerns and fertility issues surrounding testosterone replacement therapy (TRT) with the goal that the prescribing clinician understands the pathophysiology, incidence and management of each of these potential complications.

Dr. Abraham Morgentaler started the discussion with an explanation of the saturation model of testosterone on prostate cells (fig. 2). There are a limited number of androgen binding sites per cell such that at a low concentrations of testosterone (about 250 ng/dl) all those binding sites are filled, and at that point there is no longer an impact of testosterone on prostate specific antigen rise or prostate growth. As this translates to benign prostate issues there is a mild increase in prostate volume with initiation of TRT but no worsening of lower urinary tract symptoms.

The summary of data about TRT and prostate cancer is more enlightening. Citing an observational trial from Wallis et al in *Lancet* in 2016 including 38,000 men, there was a lower incidence of prostate cancer in men treated with TRT, and the greater the duration of TRT the lower the risk of prostate cancer.[1] For patients with prostate cancer after radical prostatectomy there is a single study showing a lower rate of biochemical recurrence in patients on TRT. Dr. Morgentaler highlights the notion that the historical fears about testosterone on rates of prostate cancer growth do not seem to be justified as the growing body of literature of TRT in men with prostate cancer shows reassuring results.

To address the impacts of TRT on fertility Dr. Alan Shindel reminded us that exogenous testosterone suppresses spermatogenesis and that patients should be advised of the risk of TRT on their fertility before initiation of treatment. Men who are trying to conceive should not be prescribed exogenous testosterone. For men presenting with infertility exogenous testosterone should be discontinued. Fortunately, looking at large population studies, after cessation of TRT the majority of men will recover spermatogenesis spontaneously within 6 months and almost all will recover within 2 years.

**Figure 1.** Panel discussion virtual format. Top row (left to right): Drs. Guise, Morgentaler and Shindel. Bottom row (left to right): Drs. Terlecki and Ramasamy.

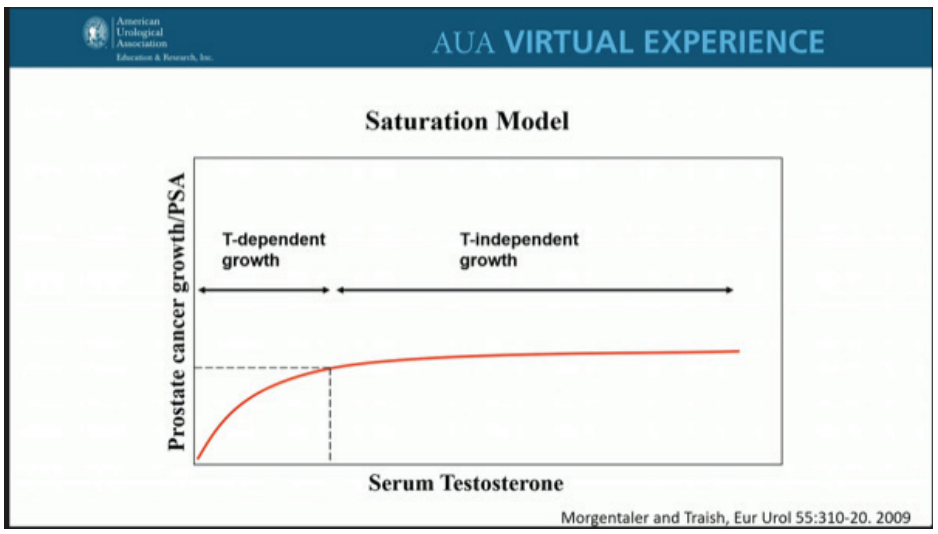


**Figure 2.** Saturation model of testosterone on prostate cells.

Potential therapeutic interventions we can attempt in order to expedite recovery include inhibiting feedback at the level of the pituitary by administration of a selective estrogen receptor modulator such as clomiphene or reducing circulating estrogen by giving an aromatase inhibitor such as anastrozole. Alternatively, you could replace gonadotropins with administration of human chorionic gonadotropin or follicle stimulating hormone to stimulate the testicles directly to make testosterone and sperm. However, Dr. Shindel concludes

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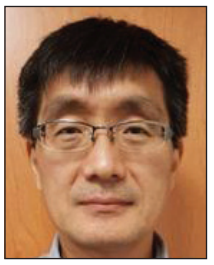
# Recurrence and Progression in Intermediate Risk Nonmuscle Invasive Bladder Cancer


Abhishek Bhat, MD | Deukwoo Kwon, PhD | Chad R. Ritch, MD, MBA

Miami, Florida

Risk stratification of nonmuscle invasive bladder cancer (NMIBC) into low, intermediate and high risk groups as indicated by the AUA/Society of Urologic Oncology (SUO) and European Association of Urology (EAU) guidelines is an important factor in determining the intensity of surveillance.[1,2] The guidelines recommend several risk based surveillance strategies using cystoscopy, cytology and cross-sectional upper tract imaging to detect recurrence in a timely manner and avoid progression.

In the AUA/SUO guidelines intermediate risk (IR)-NMIBC is a heterogenous group inclusive of primary or recurrent low grade tumors of varying size and focality, and solitary small high grade tumors with widely varying risks of recurrence and progression.[3] The recommended cystoscopic surveillance for IR-NMIBC is every 3 to 6 months with cytology and upper tract imaging every 1 to 2 years for the first 2 years. This recommendation is based on the panel's expert opinion, and the level of evidence to support specific intervals for cystoscopy is limited. Furthermore, due to the invasive nature of cystoscopy and costs to patients as well as the health system it is prudent to have reliable data to support risk stratified surveillance strategies that carefully balance these risks with the benefits of early detection.

The objective of our study was to compare 3 models of surveillance intensity for patients with IR-NMIBC during the first 2 years after diagnosis when recurrences are most common. Specifically, we created a high intensity model (3 months), a moderate intensity model (6 months) and a low intensity model (12 months) for surveillance intensity. We hypothesized that a moderate intensity model would detect recurrence in a timely manner while avoiding excessive cystoscopies.

The study was a retrospective review of our institutional NMIBC database (2010–2017) and used only patients with IR-NMIBC who had sufficient data in the form of cystoscopy, urine cytology and upper tract imaging for 2 years after diagnosis. The 3 hypothetical models for surveillance were then applied during a 2-year surveillance period after diagnosis to each patient, and we assessed when the actual recurrence had occurred relative to the interval for each model. We then

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## Managing Testosterone Therapy Complications

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that the literature does not conclusively show that either modality improves spermatogenesis any further than just cessation of testosterone supplementation.

Dr. Ryan Terlecki gave a detailed explanation of the pathophysiology of gynecomastia. It is hormone mediated proliferation of glandular subareolar breast tissue related to increased estrogenic activity due to absolute increase in estrogen or unfavorable estrogen-to-testosterone ratio. Asymptomatic gynecomastia has been reported in up to 70% of men older than 50 years old. Rates of subsequent gynecomastia after TRT has been reported as 13% to 43% in intervariable studies. Obesity is the biggest risk factor for low testosterone, which makes detection of gynecomastia complex. Confounding factors can also increase risk of gynecomastia. Those include use of 5 alpha reductase inhibitors, nutraceuticals, statins, proton pump inhibitors, spironolactone and antiretrovirals. Gynecomastia can be seen in up to half of former or current anabolic steroid users. Alcohol abuse and marijuana use are also common confounding factors. Stromal fibrosis can occur as soon as 6 months after development of symptom and typically by 2 years. If detected early before the onset of stomal fibrosis, stopping TRT should improve gynecomastia within 1 month. There are also reports of use of tamoxifen to resolve gynecomastia in 90% of patients within 90 days.

To conclude the panel discussion Dr. Ranjith Ramasamay highlighted the avoidable risk factors for polycythemia associated with TRT. According to AUA guidelines patients should have a baseline hemoglobin or hematocrit prior to initiation of TRT and therapy withheld for hematocrits greater than 50% until the etiology is explained. Erythropoiesis secondary to TRT is caused by decreased hepcidin production by the liver, exacerbation of obstructive sleep apnea and/or increased erythropoietin production by the kidney. Data suggest that longer duration of high testosterone levels may predict risk of polycythemia. Intramuscular injections and subcutaneous pellets have the highest rate of polycythemia compared to transdermal and intranasal modalities. Lower dose and higher frequency injection therapy have lower incidence of polycythemia. If the hematocrit is greater than 54%, consider phlebotomy and adjust down TRT dosing if high T levels are present. If therapeutic testosterone levels are normal or low but hematocrit is still greater than 54%, evaluation by a hematologist for further evaluation is recommended. Dr. Ramasamy highlighted the importance of screening for obstructive sleep apnea in men who develop polycythemia on TRT. ◆

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## Recurrence and Progression in Intermediate Risk NMIBC

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compared the rates of delayed detection of recurrences and avoidable cystoscopies between the models. Presence of a visible tumor on cystoscopy and/or positive urine cytology was defined as a recurrence. Any upgrading in tumor grade and/or stage was defined as progression. We assumed the reference surveillance strategy using model 1, and then determined the relative number of delayed detection of recurrence and progression if surveillance were performed using model 2 and model 3 instead.

An avoidable cystoscopy in all models was defined as cystoscopy performed with no detection of tumor. We compared the time to delay in detection of recurrence as defined by the difference between the observed actual date of recurrence and the number of months since the previous negative surveillance assessment between the models. We also calculated the cost for each model based on the Medicare allowable reimbursement rates for cystoscopy. We used 2-sample Student t-test and proportion test to compare continuous variables and proportions, respectively. All tests were 2-sided and statistical significance was considered when $p < 0.05$.

A total of 107 patients with IR-NMIBC were included in the cohort. We included only patients with recurrence within the first 2 years of diagnosis. The median age of the patients was 69 years, and median followup was 37 months. Approximately 62% were high grade, 38% were low grade and the majority were stage Ta (97.6%) at diagnosis. There was a total of 66 (77.6%) recurrences and 12 (14.1%) episodes of progression during the followup period. Relative to model 1 there were 33 delayed detections of recurrence in model 2 and 41 delayed detections of recurrence in model 3 with no statistical difference between model 2 and model 3 (p=0.22). With respect to time to delay in detection of recurrence there was a 1.68-month mean delay for model 1 vs 3.18 months for model 2 and 7.55-month delay for model 3 (p <0.001 model 1 vs model 2, p <0.001 model 2 vs model 3; figs. 1 through 4). With respect to progression, relative to model 1 there were 8 delayed detection of progression events in model 2 and 9 delayed detection of progression events in model 3 with no statistical difference between model 2 and model 3 (p=1). Of those who progressed there were no deaths from bladder cancer and none required radical cystectomy. The mean number of avoidable cystoscopies through 2 years was higher in model 1 (2.05) vs model 2 (1.32) and model 3 (0.2) (p=0.0174 model 1 vs model 2, p <0.001 model 2 vs model 3). As expected, cystoscopic surveillance cost was more with model 1 with an overall cost of $4,448 through 2 years vs model 2 ($2,224) and model 3 ($1,122) based on current Medicare reimbursement rates.

We conclude that adherence to the present AUA/SUO guidelines for surveillance in patients with IR-NMIBC is associated with timely detection of recurrences and progression. However, relative to the 3-month interval a moderate intensity 6-month surveillance interval appears to be appropriate for IR-NMIBC in the first 2 years of diagnosis based on the low number of delayed detection of recurrences, short time to delay in detection, absence of clinically significant progression, and considering the high rate of avoidable cystoscopy and associated costs.

Limitations of the study are the retrospective nature and the use of hypothetical models as opposed to a prospective real-world surveillance protocol comparison. Furthermore, the surveillance intervals actually used to detect tumors

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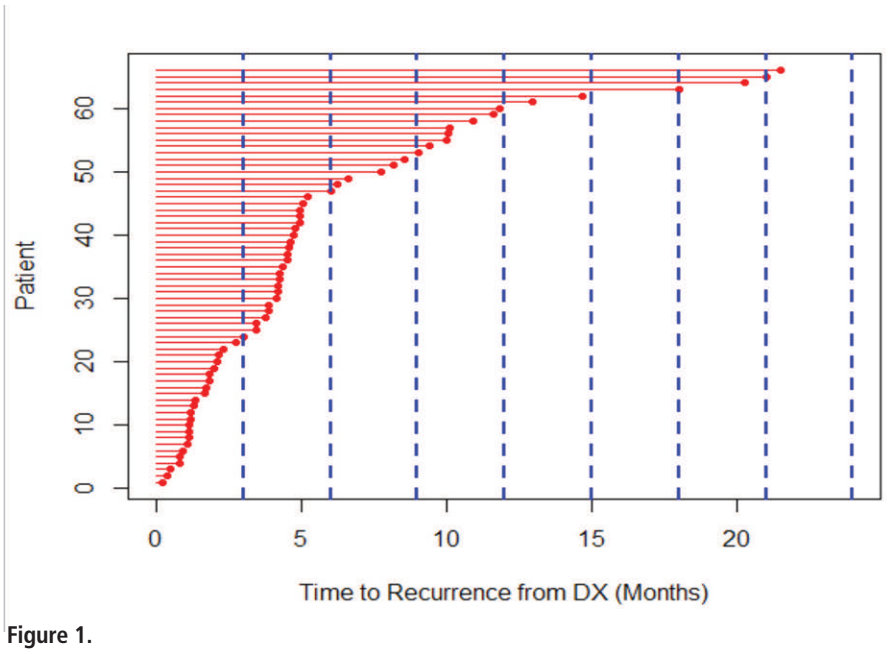


Figure 1.

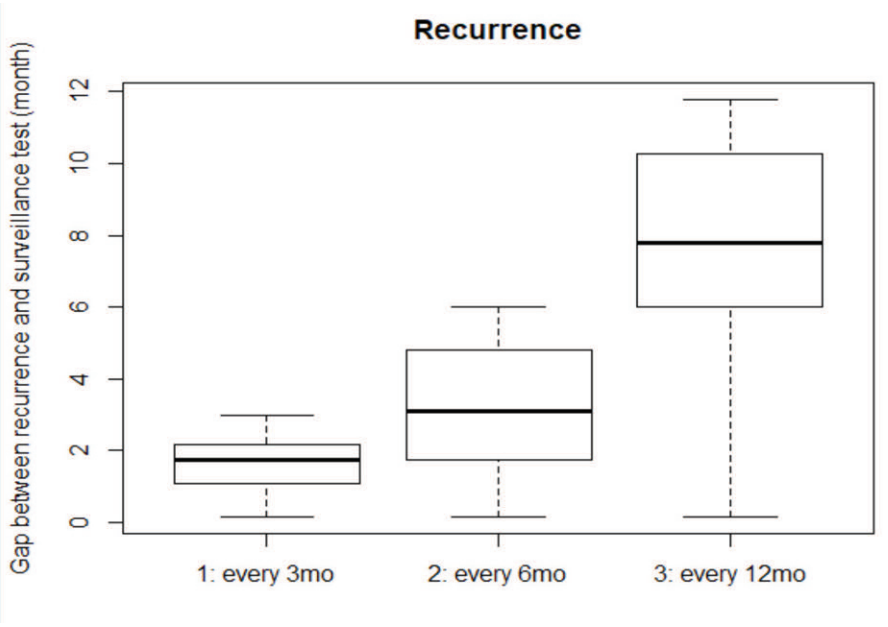


Figure 2.

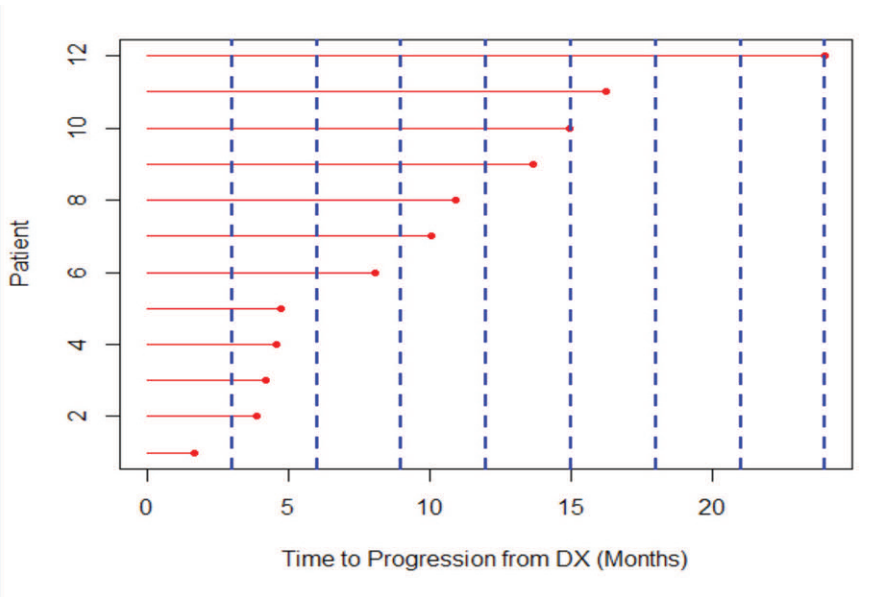


Figure 3.

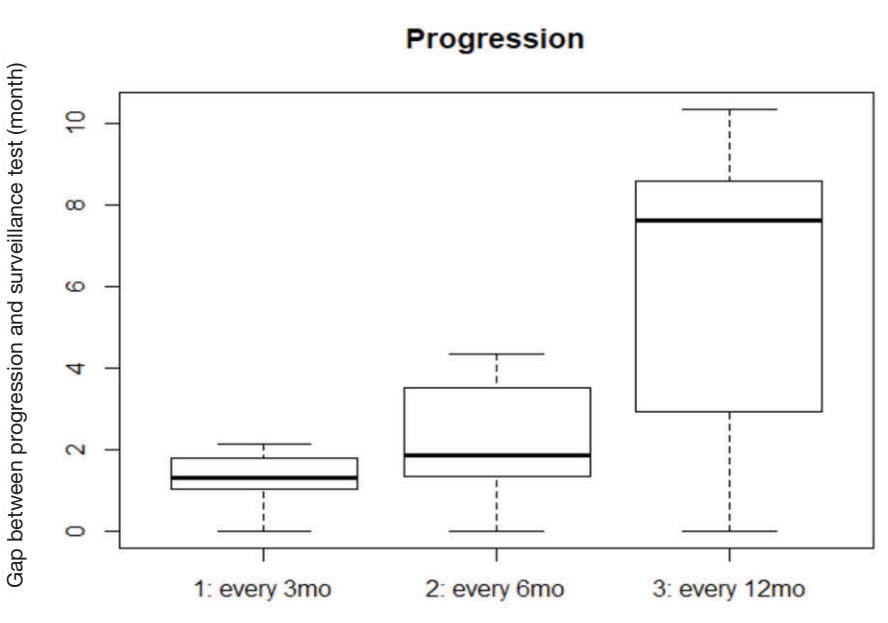


Figure 4.

## Recurrence and Progression in Intermediate Risk NMIBC

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were based on urologist discretion and we cannot rule out additional delays in detection of recurrence. To our knowledge, this study is the first to investigate and recommend a specific surveillance interval in IR-NMIBC. Recently, Schroeck et al studied cystoscopy frequency in low risk NMIBC and found that more frequent cystoscopy did not decrease the risk of progression or death, and was associated with increased use of transurethral resection.[4] Our study similarly suggests that a 6-month surveillance interval is appropriate for IR-NMIBC vs 3-month or 12-month without compromising oncologic outcomes and may avoid additional costs to the health care system. Further research prospectively evaluating a 6-month surveillance strategy in the first 2 years after diagnosis is necessary to determine whether this approach should become the standard in IR-NMIBC.

*AUA 2020 Virtual Science Best Poster winner.* ◆


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# The Rapid Access Prostate Imaging Diagnostic Pathway


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### Introduction

We set up the Rapid Access Prostate Imaging and Diagnosis (RAPID) pathway (fig. 1) to streamline and improve clinical outcomes for men undergoing prostate cancer diagnostics as a way of delivering the findings of PROMIS.[1] We introduced same day diagnostic multiparametic (mp) magnetic resonance imaging (MRI) and transperineal biopsies with those having a nonsuspicious mpMRI being discharged back to their primary care physician with an ad personam prostate specific antigen (PSA) level (based on baseline PSA density calculated using MRI volume). The new pathway was designed in keeping with the advantages of performing MRI before biopsy and of a mpMRI targeted biopsy strategy.[1–4]

Before developing the RAPID pathway our group completed a comprehensive analysis of outcomes in the existing prostate cancer pathway (fig. 2). We identified a number of problems. First, the pathway was inefficient. Patients had to attend multiple appointments, most commonly 4. Many men were also waiting more than the United Kingdom standard of 28 days for their cancer diagnosis. Second, almost all biopsies performed were systematic transrectal (TRUS). We know this approach misses up to 50% of significant cancer. Some centers were performing pre-mpMRI but not always with dedicated targeted cores. Third, a significant proportion of our patient group was being diagnosed with clinically insignificant low risk disease with a low chance of affecting life expectancy. Fourth, we found that post-biopsy urinary tract infection and sepsis occurred in 2% to 4% of cases. Some of these men unfortunately required admission to intensive care. Herein, we report the updated outcomes of the "one-stop" RAPID pathway introduced across 3 hospitals since its introduction.

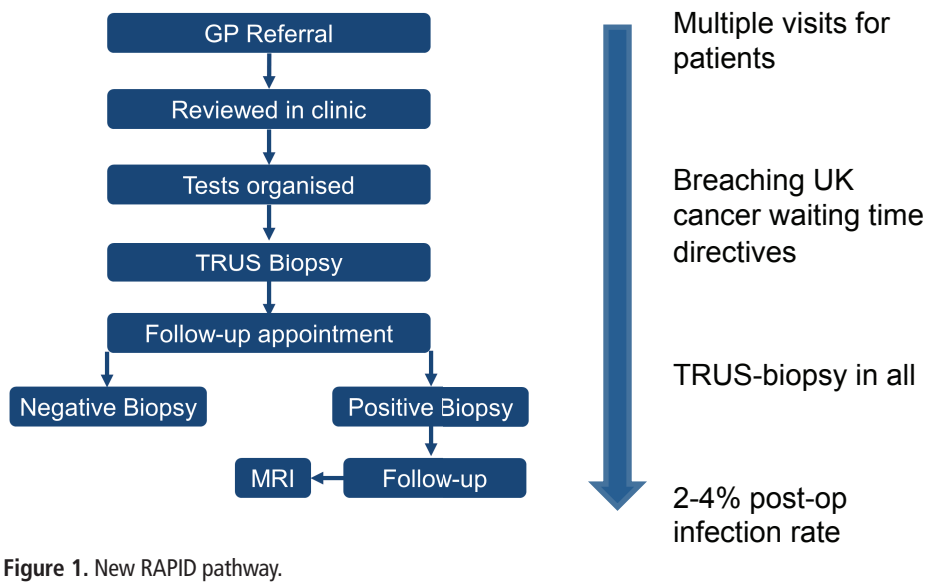


**Figure 1.** New RAPID pathway.

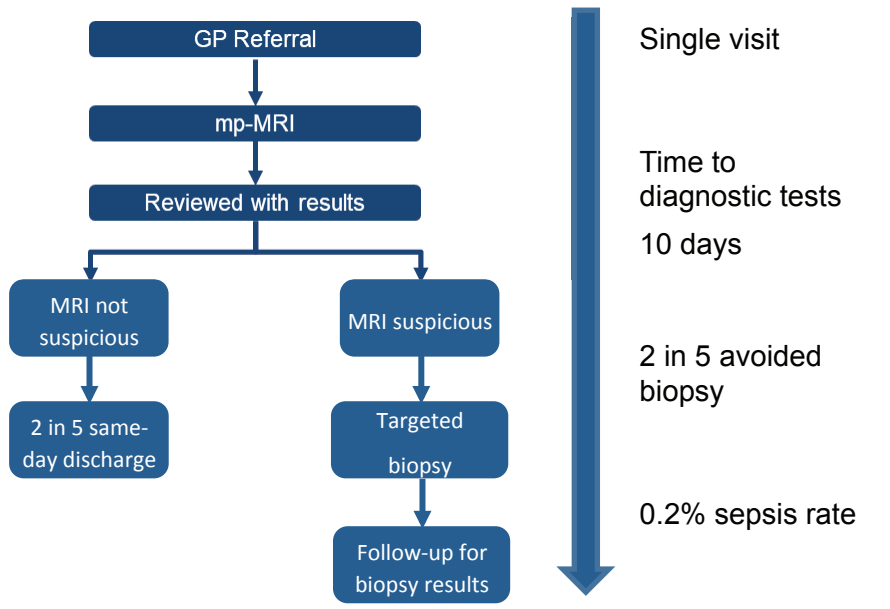


**Figure 2.** Original prostate cancer diagnostic pathway.

### Patients and Methods

A total of 1,719 patients were referred into the RAPID pathway between April 2017 and July 2019. Patients received an appointment for mpMRI and clinical review on the same day. Same day discharge occurred if the mpMRI was nonsuspicious with the patient told of the low risk of still harboring clinically significant prostate cancer. A transperineal prostate biopsy (TP-Bx) was offered if the mpMRI score was 4 or 5. A score of 3 required a PSA density of 0.12 or more although discretion is allowed by clinician and patient. This was performed as a day case under local anesthetic and antimicrobial prophylaxis. Biopsies involved targeting up to 3 suspicious lesions (4–8 cores per target) and carrying out nontargeted systematic biopsies with the latter not overlapping with the targeted areas. Significant prostate cancer was defined by a Gleason grade of 3+4 or greater.

### Results

The median age was 66 (IQR 60–72), PSA 6.7 (IQR 4.9–9.9) and median time from referral to mpMRI with or without biopsy was 9 (IQR 6–13) days.

There were 810 of 1,719 (47%) men with a nonsuspicious mpMRI, and 46 (6%) of these 810 men underwent biopsies. We found cancer in 19 of 810 (2%) and significant cancer in 5 of 810 (1%) of these men.

There were 836 of 1,719 (49%) men with a suspicious mpMRI. All of these men went on to have a TP-Bx. There were 638 of 836 (76%) men subsequently diagnosed

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## RAPID Pathway

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with any prostate cancer and 456 of 836 (54%) with clinically significant prostate cancer. Of the patients with a negative TP-Bx 60 of 198 (30%) had known causes of mpMRI false-positives such as inflammation or atrophy. A flow chart of these diagnostic outcomes of the combined mpMRI and TP-Bx is shown in figure 3.

Complications after transperineal biopsy were rare, as 7 of 836 (0.8%) developed acute urinary retention, 3 of 836 (0.36%) required catheterization for bleeding and 1 of 836 (0.12%) had culture proven urinary tract sepsis.

### Discussion

Optimal prostate cancer diagnostic pathways should demonstrate maximal significant cancer detection, minimal insignificant cancer detection and a minimal repeat biopsy rate. They should also diagnose men in good time. After the introduction of RAPID the time from referral to biopsy decreased to 10 days.

mpMRI has demonstrable advantages when it comes to localizing discrete cancer lesions within the prostate.[1] Its widespread adoption has allowed image guided prostate biopsy strategies to be contemplated. We now know that an image targeted approach improves significant cancer detection rates while minimizing the diagnosis of indolent cancers.[2,3] It was with this in mind that the RAPID pathway was developed.

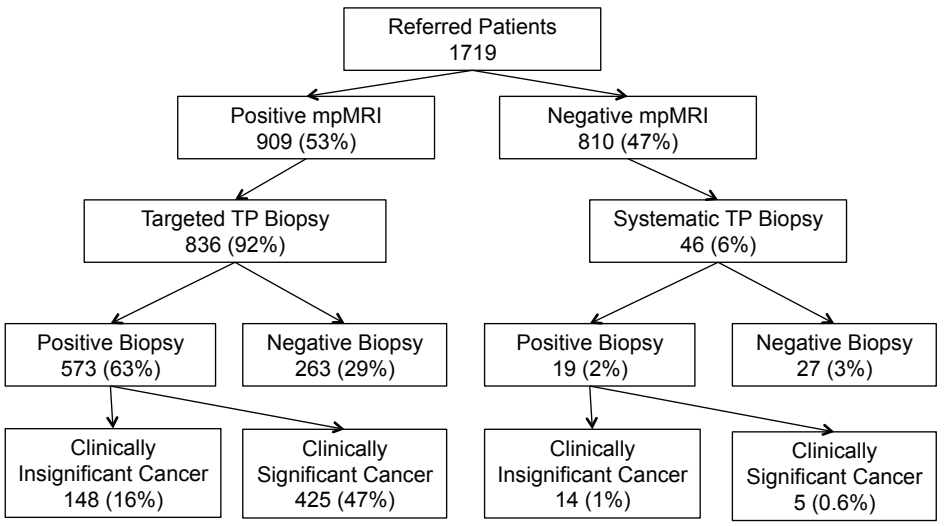


**Figure 3.** Diagnostic outcome flowchart of men entering RAPID pathway.

After the introduction of RAPID we saw a significant increase in the proportion of diagnosed significant cancers in men biopsied at 47% compared to 23% under the old pathway. The proportion of indolent cancers diagnosed also decreased to 8% from 12% under the old pathway. A mpMRI first approach also allowed 2 in 5 men to avoid a biopsy.

An area of debate is whether not sampling "normal" areas of the prostate risks missing significant cancer. This risk is unlikely to be any higher than 1 minus the negative predictive value of mpMRI for detecting such disease (in other words, around 20%).[1] The real question is what is the risk of missing significant disease in men with a lesion on mpMRI that is biopsy negative? Again, it is unlikely to be any higher than the aforementioned figure especially in the absence of independent risk factors such as a positive family history or high PSA density. Alternatively if a targeted biopsy is negative is it reasonable to be more concerned with potentially missed significant cancer outside of a mpMRI lesion when significant cancer in the lesion may have been genuinely missed? If the latter is of greater concern we know that a false-negative rate due to procedural error is mitigated by increasing biopsy density.[3]

Regardless, the risk of missing significant cancer in this group of men seems exceptionally low. In our RAPID group 46 of 810 (6%) of men referred had a nonsuspicious mpMRI but underwent TP-Bx due to risk factors or personal choice. Clinically significant disease was extremely low in this group of men at 0.6% of all with nonsuspicious mpMRIs. In those without risk factors the rate is likely to be even lower.

### Conclusions

The RAPID pathway is safe and effective for diagnosing suspected prostate cancer. Our MRI triage approach allows 2 in 5 men to avoid an immediate biopsy. Half of men who undergo biopsy have clinically significant disease.

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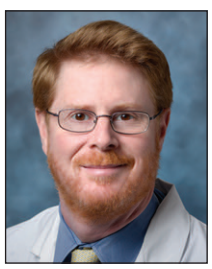
# Misdiagnosis of Interstitial Cystitis: Rates and Reasons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Interstitial cystitis/bladder pain syndrome (IC/BPS) is defined by the Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction (SUFU) as "an unpleasant sensation (pain, pressure, and discomfort) perceived to be related to the urinary bladder associated with lower urinary tract symptoms of more than 6 weeks duration, in the absence of infection or other identifiable causes."[1] There is significant diagnostic uncertainty of IC/BPS. This is due to the lack of a definitive diagnostic test for IC/BPS as well as a lack of definite diagnostic criteria for IC/BPS.

Diagnosis is a key challenge in managing the disease as it is essentially a diagnosis of exclusion. Misdiagnosis may result from the failure to recognize a separate underlying condition that would explain symptoms (incorrectly assigning a diagnosis of IC/BPS) or vice versa (incorrectly assigning a separate diagnosis when the true clinical picture is IC/BPS). Making the distinction between IC/BPS and other benign conditions is not always straightforward as there is significant overlap (eg urinary frequency may be present in overactive bladder and IC/BPS).

These challenges in diagnosis make the true prevalence of IC/BPS notoriously difficult to estimate. For example, the prevalence of IC/BPS for women in the literature has ranged from as low as 0.045% in administrative claims data to 6.5% in a population based telephone study.[2]

This translates to an approximately twentyfold range in prevalence estimates of IC/BPS in women and an approximately eightfold range in men (based on administrative studies alone). When combining survey and administrative studies there is an astounding 150-fold range in prevalence estimates for women and a greater than 500-fold range for men. These wide ranges in prevalence estimates suggest that IC/BPS is likely frequently misdiagnosed (either under or over diagnosed). In this study we used a national data set to assess the reasons for misdiagnosis of IC/BPS by primarily assessing whether an ICD code for IC/BPS truly represents IC/BPS. Furthermore, we sought to identify patients who truly met IC/BPS diagnostic criteria but were never assigned an ICD code

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## Misdiagnosis of Interstitial Cystitis

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for IC/BPS.

The Veterans Affairs Informatics and Computing Infrastructure (VINCI) was used to identify all living patients in the Veterans Affairs (VA) system between 1999 and 2016 who had an ICD-9/10 code for IC/BPS (9,503, 595.1/ N30.10). Further identified were patients with ICD codes for "IC/BPS-like" conditions, which were defined as conditions that are frequently misdiagnosed for IC/BPS (prostatitis, vagismus, vulvar vestibulitis, vulvodynia and dyspareunia). All other patients were considered controls (5,346,866). A key advantage of the VINCI database is that it combines the scope of a large population based administrative database with in-depth chart abstraction.

To assess the accuracy of an ICD code for IC/BPS representing true IC/BPS as well as cases of true IC/BPS that were potentially missed, random and balanced samples of patients were selected from those with an ICD code for IC/BPS, those with an "IC/BPS-like" code and controls. In-depth chart review was performed on these samples to determine who actually met diagnostic criteria for IC/BPS (see Appendix). If a patient's medical record was not sufficient to make a determination the diagnosis was considered equivocal. Patients were excluded if they had concomitant conditions that would make it difficult or impossible to assess the true presence of IC/BPS. These conditions included a history of cancer (aside from nonmelanoma skin cancers), dementia, HIV, cystectomy or if the patient was deceased at the time of query. If chart abstraction revealed that a patient did not meet criteria for IC/BPS, the actual diagnosis or reason for not meeting IC/BPS diagnostic criteria was determined.

In-depth chart abstraction revealed that of the 1,334 patients with an ICD code for IC/BPS only 48.8% met diagnostic criteria for IC/BPS. The most common single reason for not meeting criteria was the lack of pain or discomfort as a symptom followed by the existence of another condition that explained the symptoms. A total of 11 (4.0%) and 4 (0.6%) patients from the IC/BPS-like and control groups, respectively, met criteria for true IC/BPS (see figure).

Our findings here highlight the high rates of misdiagnosis of IC/BPS. Misdiagnosis frequently occurred when an ICD code for IC/BPS was assigned to patients who did not actually meet true IC/BPS criteria. Furthermore, although the rates of true IC/BPS for patients with an IC/BPS-like code or controls appear low (4.0% and 0.6%, respectively), given the large cohorts sampled these low percentages actually translate to a large number of patients potentially suffering from IC/BPS who are not properly identified. For example, if extrapolated our results would suggest that there are more than 35,000 patients in the VA system who meet IC/BPS criteria but are not identified.

Our study suggests that the inaccuracy of the diagnosis of IC/BPS stems from misclassifying patients as having IC/BPS when it is not actually present and failing to identify cases where IC/BPS is truly present. Crudely, our results suggest that an ICD code for IC/BPS is associated with a low positive predictive value (only 48.8% of those with an ICD code actually met diagnostic criteria) and low sensitivity (12.5%).

Future directions will involve the development and implementation of strategies to improve the accuracy of the identification of patients suffering from IC/BPS and further improving treatment modalities and outcomes.

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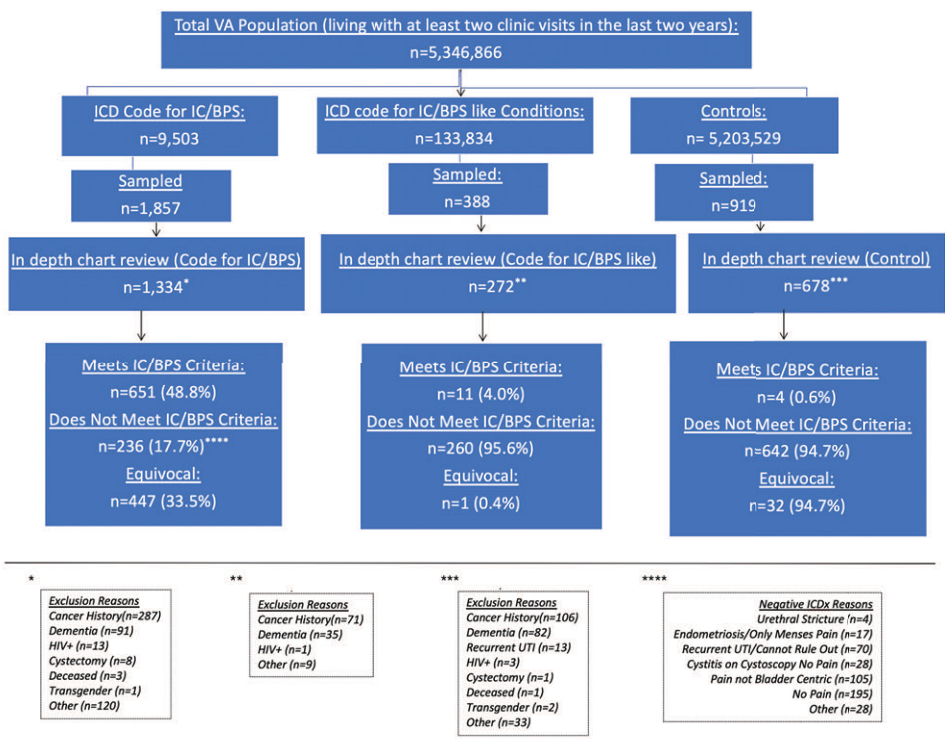


**Figure.** Consort diagram of rates of and reasons for misdiagnosis of IC/BPS in large national cohort.

**Appendix.** Diagnostic criteria for IC/BPS.

Patients who were a correct IC/BPS diagnosis met at least one of the following criteria:

1. Two visits (in the VA system) complaining of unpleasant *bladder centric* sensation in the absence of positive urine culture at least 6 weeks apart.
2. One visit complaining of bladder centric pain/unpleasant bladder centric sensation and a second visit complaining of "likely" IC/BPS-related pain in the absence of positive urine culture at least 6 weeks apart (both at the VA). We defined "likely" IC/BPS-related pain as pain that could be due to IC/BPS but without a specific complaint of bladder-centric pain or bladder tenderness on exam. Symptoms of "likely" IC/BPS include dysuria, pelvic pain, chronic lower abdominal pain, dyspareunia.
3. A history of bladder pain and/or a history of IC/BPS (in the VA or other system) with one additional visit complaining of bladder centric pain in the absence of a positive urine culture.

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# Is Ureaplasma/Mycoplasma Colonization Negatively Associated with Chronic Urinary Symptoms?

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Irritative lower urinary tract symptoms (LUTS) such as urinary frequency, urgency and dysuria contribute to a significant burden of illness and are disruptive to quality of life (QOL). When LUTS are present without a positive culture or persist despite appropriate treatment, understanding their etiology can be challenging. Many providers evaluate such patients for the atypical organisms *Ureaplasma/Mycoplasma*, and testing for these atypical microbes remains quite common. At our institution alone 575 *Ureaplasma/Mycoplasma* tests were run in 2019. While *Ureaplasma/Mycoplasma* infections are most common in individuals younger than 25 years of age, 64% of these tests were ordered for patients older than 65 years (fig. 1). The most common indications were benign prostatic hyperplasia in men and urinary tract infection in women. Only 2% were done for indications clearly linked to *Ureaplasma/Mycoplasma* such as pelvic inflammatory disease (PID), urethritis or infertility.

Currently, the European STI (Sexually Transmitted Infections) Guidelines recommend against testing for *U. urealyticum*, *U. parvum* and *M. homini* even in symptomatic men and women.[1] This recommendation is based on a lack of evidence demonstrating a benefit. While it seems clear that certain *Mycoplasma* and *Ureaplasma* species may be associated with nongonococcal urethritis particularly in young men, the current clinical use of *Ureaplasma/Mycoplasma* testing is primarily to evaluate chronic urinary symptoms in the absence of signs of acute infection.

There is little evidence linking these microbes to other less specific genitourinary symptoms. Previous studies have demonstrated high rates of *Ureaplasma/Mycoplasma* positivity in women with chronic voiding symptoms and found that symptoms improved with antibiotic treatment in positive patients. However, these studies did not compare these positive, symptomatic patients to those who tested negative or who were positive but without symptoms. In fact, asymptomatic controls exhibited even higher rates of positivity than symptomatic patients. Controlled prevalence analyses failed to demonstrate associations of *Ureaplasma/Mycoplasma* with urinary symptoms,

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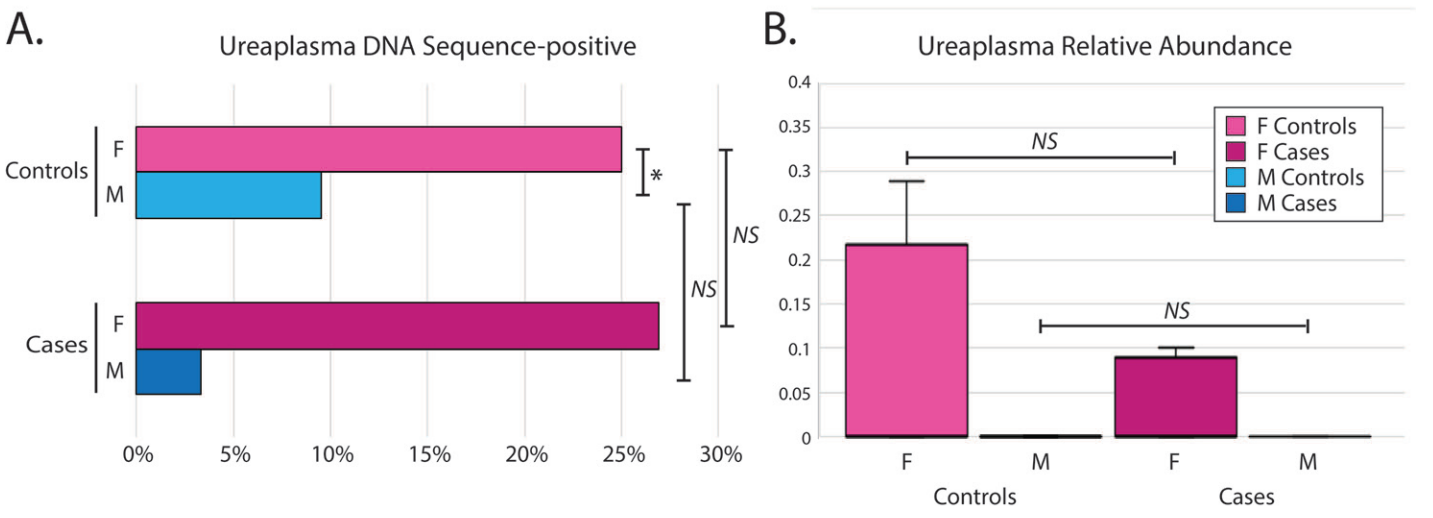


**Figure 2**. *Ureaplasma* levels differ between men and women. There are significant differences in frequencies of organisms in men and women but no differences between gender matched subjects with and without symptoms (*A*). Median relative abundance of *Ureaplasma* spp. (*B*) revealed trend toward increased abundance in asymptomatic patients but was not significant (NS). Asterisk indicates p=0.03

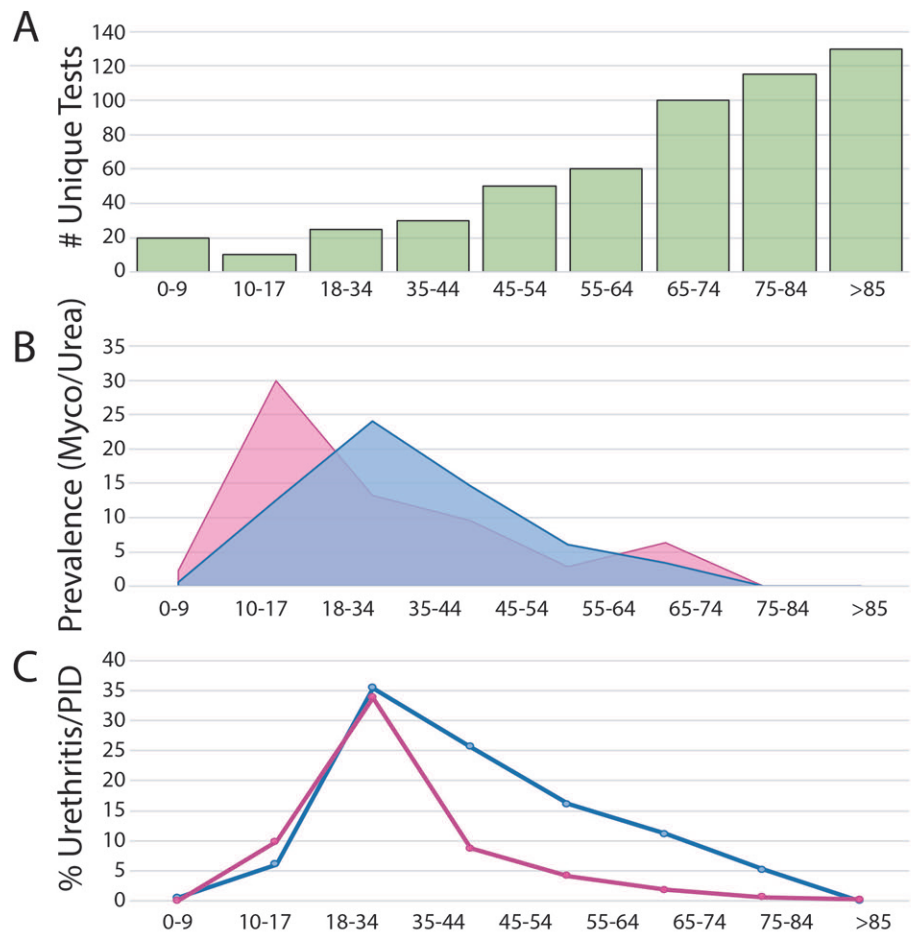


**Figure 1.** Frequency of *Ureaplasma* and *Mycoplasma* testing at our institution, with (*A*) number of unique tests ordered by patient age, (*B*) prevalence of positive tests by patient age and (*C*) proportion of patients with urethritis or PID diagnosis by patient age.

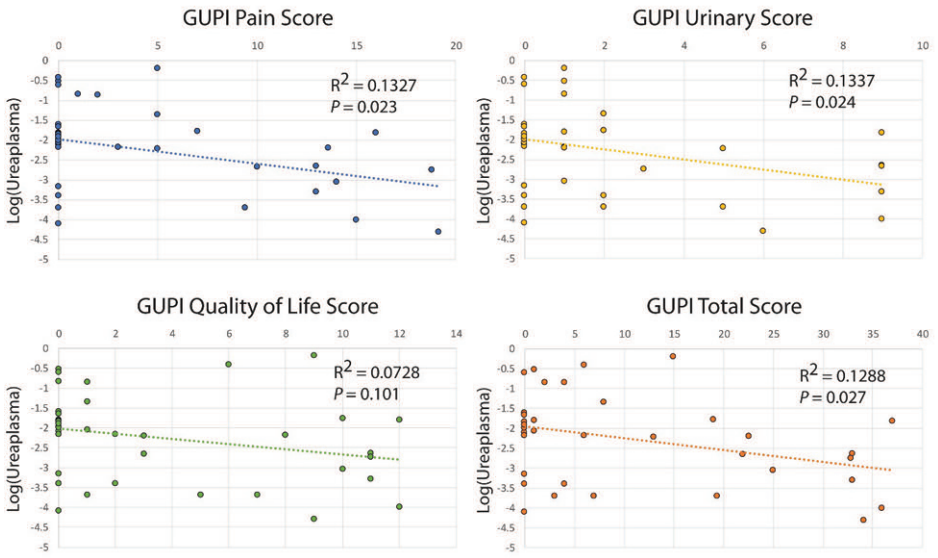


**Figure 3.** *Ureaplasma* concentrations are inversely correlated with lower urinary tract symptoms. Domains on Genitourinary Pain Index (GUPI) as well as total GUPI score are plotted against log of concentration of *Ureaplasma* DNA determined by qPCR.

## Ureaplasma/Mycoplasma Colonization

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particularly those indicative of urinary infection such as urinary frequency and dysuria.

Furthermore, *Ureaplasma/Mycoplasma* colonization is common and frequently seen in association with infection by other genitourinary pathogens such as *Chlamydia trachomatis* and bacterial vaginosis, so the improvements noted after antibiotics in uncontrolled studies may reflect resolution of infection with other pathogens.[2,3] In addition, followup cultures after treatment show resolution of *Ureaplasma/Mycoplasma* colonization in 43% to 95% of subjects with subsequent reinfection or persistence being common and symptomatic improvement demonstrating little correlation with eradication. As such, significant confusion still exists around whether *Ureaplasma/Mycoplasma* testing in chronic irritative urinary symptoms is useful.

To our knowledge, no study has compared the *Ureaplasma/Mycoplasma* colonization in patients with chronic irritative urinary symptoms to asymptomatic controls using current clinical testing paradigms. Therefore, we sought to explore the association of *Ureaplasma/Mycoplasma* species with irritative LUTS using next generation sequencing (NGS) and quantitative polymerase chain reaction (qPCR) methods in patients with chronic irritative urinary symptoms who also had negative clinical urine cultures and lacked other signs of acute infection on history and exam (urethral/cervical discharge or substantial pyuria) and asymptomatic subjects.

Of 179 subjects only 3 subjects had detectable *Mycoplasma* (2 female, 1 male) and all were asymptomatic. A much higher number of subjects carried *Ureaplasma* (approximately 25% of women), but there were no significant differences between symptomatic and asymptomatic subjects for *Ureaplasma* positivity (fig. 2, *A*, p=0.87 for females and p=0.91 for males). There was also no significant difference in the relative proportion of *Ureaplasma* (fig. 2, *B*, females p=0.48 and males p=0.62), but we noted a trend toward lower concentrations in symptomatic subjects than controls. In the subset of *Ureaplasma* positive subjects linear regression analysis of the 43 subjects with detectable *Ureaplasma* in their urine revealed that *Ureaplasma* concentration was negatively related to urinary symptoms (fig. 3).

Finally, we explored the correlation among urethral pain, dysuria, or urinary frequency and *Ureaplasma spp.* concentrations by qPCR (fig. 4, *A*). Subjects with urethral pain and dysuria each trended toward lower concentrations of *Ureaplasma spp.* with the negative correlation reaching statistical significance (p=0.02) for urethral pain. The severity of urinary frequency in particular, a common indication prompting an evaluation for *Ureaplasma/Mycoplasma,* did not correspond to higher relative abundance of *Ureaplasma spp.* (fig. 4, *B*).

To our knowledge, no study has compared the *Ureaplasma/Mycoplasma* colonization in patients with chronic irritative urinary symptoms to asymptomatic controls using current clinical testing paradigms.

Therefore, using high throughput sequencing and quantitative molecular diagnostics we demonstrated a high frequency of genitourinary tract colonization with *Ureaplasma* for asymptomatic subjects and those with chronic urinary symptoms. Despite high detection rates there was a negative correlation of *Ureaplasma* with all urinary symptoms assessed. While detection frequencies differed between men and women, this negative association persisted in both genders. The data clearly demonstrate that there is no clinically significant association of *Ureaplasma* or *Mycoplasma* with irritative urinary symptoms in the absence of substantial pyuria.

Most studies demonstrating positive associations of *Ureaplasma/Mycoplasma* with genitourinary symptoms examine populations with clear infectious symptoms. We believe that over time the association of atypical bacteria such as *M. genitalium* and *U. urealyticum* with clinical urethritis may have

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## Ureaplasma/Mycoplasma Colonization

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been conflated to support a role for all *Ureaplasma* and *Mycoplasma* in any urinary symptoms, even in the absence of evidence for infection. Our report adds state-of-the-art sequencing data and quantitative molecular diagnostics to support the current guidelines that recommend against routine testing for *Mycoplasmataceae* in patients with urinary symptoms with a low pretest probability for true urethritis. Such testing is likely to result in potentially harmful overtreatment without addressing the true etiology of patient symptoms.

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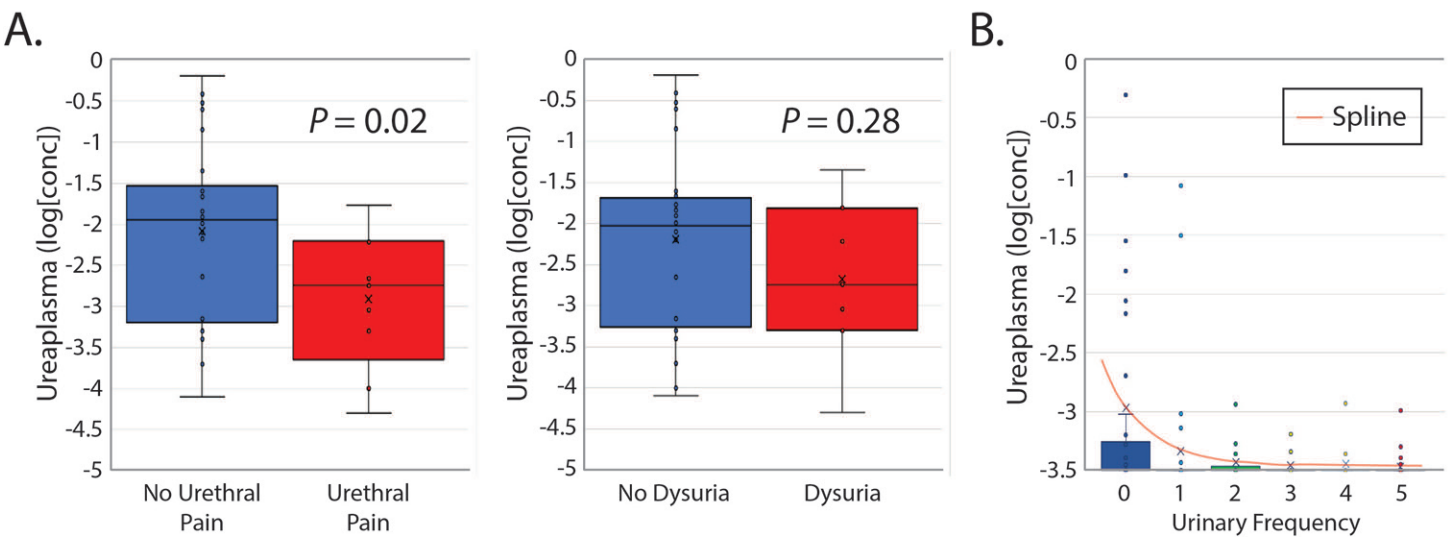


**Figure 4.** Urethritis associated symptoms are not associated with increased *Ureaplasma* concentrations. *A*, *Ureaplasma* levels were compared for groups with and without symptoms. Trend was for lower concentrations in symptomatic group. *B*, severity of urinary frequency, measured by 6-point Likert scale, plotted against *Ureaplasma* levels again noted inverse correlation between symptoms and bacterial concentration.

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# Fluoroquinolone Prescriptions Increase Despite FDA Warnings

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**Quoc-Dien Trinh, MD**
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Antibiotic stewardship remains critical as rates of antibiotic resistance rise partly due to indiscriminate prescribing habits.[1] The United States Food and Drug Administration (FDA) added boxed warnings to all fluoroquinolones in 2008 and 2013 describing the increased risk of tendon rupture and irreversible peripheral neuropathy, respectively. Mounting evidence confirming the severity and frequency of these adverse effects prompted the FDA in 2018 to issue a drug safety communication recommending against the use of fluoroquinolones for acute sinusitis, acute bronchitis and uncomplicated urinary tract infections (UTIs).[2]

While several studies have described general trends in antibiotic prescribing habits in recent years none have assessed the effect of the FDA warnings on fluoroquinolone prescribing habits. We used the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS) to assess changes in fluoroquinolone prescription patterns for sinusitis, UTI and bronchitis following the FDA safety warnings.

We queried the NAMCS and NHAMCS to identify all patients presenting between 2006 and 2015 and prescribed a fluoroquinolone for a primary diagnosis of bronchitis, UTI or sinusitis. The association between the release of the FDA warnings and outpatient fluoroquinolone prescribing habits was assessed with an interrupted time series model estimating patient odds of prescription during each study period. Subgroup analyses assessing condition and antibiotic specific trends were also performed.

We identified 16,040 encounters (weighted 199,591,348) during the 10-year period. The adjusted odds of receiving a fluoroquinolone prescription in an encounter for sinusitis, bronchitis or UTI was 0.09 (95% CI 0.09–0.09) in the first period vs 0.08 (95% CI 0.06–0.09) in the second period after the FDA warning about tendon rupture (p=0.4). The odds of fluroquinolone prescription increased by 70% to 0.13 (95% CI 0.06–0.23) in the third period after the FDA warning regarding irreversible neuropathy (p=0.003, see figure). A subgroup analysis comparing condition specific trends in fluoroquinolone prescribing revealed receipt of a fluoroquinolone for sinusitis dropped over the study period (2.8%, 95% CI 1.0–7.6 vs 2.9%, 95% CI 0.7–10.7, p=0.3), whereas rates of fluoroquinolone prescribing for a diagnosis of urinary tract infection (16.3%, 95% CI 9.1–23.4 vs 10.8%, 95% CI 8.6–13.0, p=0.03) or bronchitis (9.2%, 95% CI 2.8–15.6 vs 4.8%, 95% CI 3.7–6.0, p=0.04) increased significantly between periods 2 and 3.

In an analysis of 199 million weighted ambulatory and emergency department encounters for sinusitis, bronchitis and UTI, we found that FDA warnings regarding potential side effects of fluoroquinolones were not associated with a decrease in prescriptions, and in fact the odds of prescription increased significantly after the 2013 warning. The most pronounced increases were noted among individuals with a diagnosis of urinary tract infection suggesting that urologists and primary care physicians alike must be more judicious with their prescribing habits.

The precise etiology of this apparent disregard for FDA boxed

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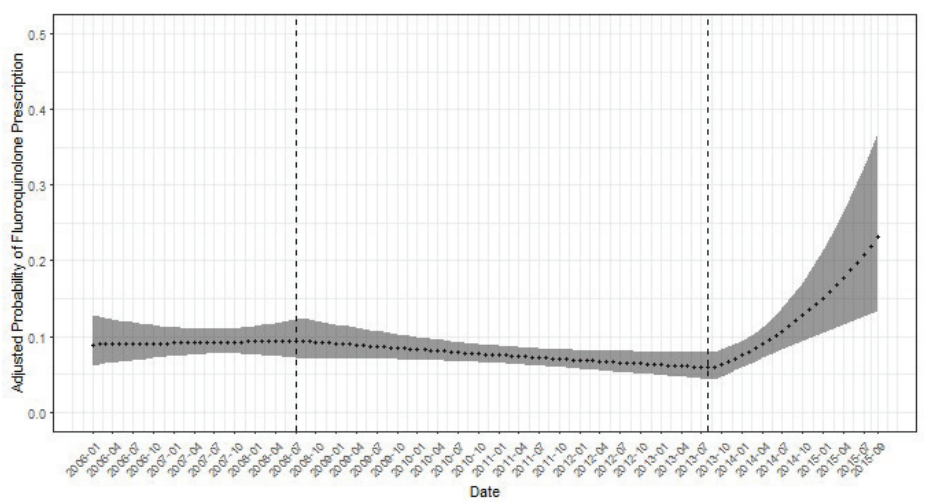


**Figure.** Adjusted probability of receipt of fluoroquinolone prescription across time. Shaded area indicates 95% CI.

## Fluoroquinolone Prescription Increase

▼ Continued from page 22

warnings, and by proxy potential solutions, remains nebulous. One possibility is that physicians are simply unaware of these warnings, as evidenced by studies assessing the effect of FDA warnings regarding suicidality for anti-epileptic and antidepressant prescriptions, which demonstrated that approximately 20% to 30% of physicians surveyed were unaware of major FDA drug safety warnings. Notably, 80% of those who were aware planned to change their prescription patterns suggesting that campaigns aimed at more widely touting FDA warnings may represent an avenue by which to influence prescribing patterns.[3]

Our findings are also notable for the significant variability with which fluoroquinolones were prescribed for the 3 conditions assessed during our study, with urinary tract infection again serving as the outlier. The fact that fluoroquinolone prescribing rates among patients with a diagnosis of urinary tract infection ranged so widely suggests that this condition and accompanying management strategy is ripe for care standardization. Consequently, touting evolving society specific guidelines regarding appropriate antibiotic prescribing habits such as those being advanced by the American Urological Association represents yet another mechanism by which to achieve more judicious antibiotic prescribing habits that address rising resistance patterns and recently recognized adverse effects.[4,5]

*AUA 2020 Virtual Science Best Poster winner.* ◆

Quoc-Dien Trinh reports personal fees from Astellas, Bayer, Janssen and Intuitive Surgical and is supported by a Health Services Research pilot test grant from the Defense Health Agency and an unrestricted educational grant from the Vattikuti Urology Institute. David F. Friedlander was supported by a National Institutes of Health T32 training grant (2T32DK007527-33).

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# Robot-Assisted Renal Transplantation: Is it Ready for Prime Time?

**Alp Sener, MD, PhD, FRCSC**
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There is a worldwide increase in the number of patients with end stage renal disease requiring transplantation. Insurmountable evidence suggests that renal transplantation is the most optimal mode of renal replacement therapy compared to dialysis. It is also very clear that transplantation portends a significant improvement in medical outcomes primarily through the reduction in cardiovascular morbidity with a significant increase in patient survival while at the same time decreasing the overall cost to the health care system.

Until recently open renal transplantation was considered the treatment modality of choice by all transplant programs worldwide. However, as with many other facets of urological surgery, innovation has led to a surge in the number of programs performing robot-assisted renal transplantation. The pioneering role of urologists in surgical innovation especially in the field of transplantation is not new. The first living donor nephrectomy and transplant were successfully performed by Drs. Harrison and Murray in 1954. The eventual developments in minimally invasive laparoscopic surgery then led to the first laparoscopic donor nephrectomy 25 years ago, which then opened the doors for other significant advances such as laparoendoscopic single site donor nephrectomy surgery, which was then further advanced with the introduction of robotic platforms, which were also mostly urologist driven. It was inevitable that eventually urologists would apply robotic assisted techniques to master the complex vascular reconstruction required in renal transplantation.

Although there is general consensus regarding the multitude of advantages of minimally invasive techniques in surgery, the use of the robotic assisted platform in kidney transplantation continues to be debated amongst all transplant surgeons regardless of whether their training is in urology, general surgery or vascular surgery. We were fortunate to virtually debate this growing trend at AUA2020 with 2 experts in renal transplantation and minimally invasive robotic surgery: Dr. Ken Pace, Vice Chief of Surgery and Chief of the Division of Urology at St. Michael's Hospital in Toronto, Canada and Dr. Alberto Breda, the Head of Uro-Oncology and Director of Kidney Transplant Surgery at the Universitat Autònoma in Barcelona, Spain.

Dr. Pace argued that the technique of open kidney transplantation has been clearly improved over decades and has been shown to have excellent short-term and long-term patient and graft survival outcomes. Several factors, including the ability to control the warm reimplantation time, capacity to facilitate multiple learners (from novice to expert) to participate in the various aspects of the case and the already established low rates of acute graft loss due to technical factors including arterial thromboses, all support the continued use of the open approach for kidney transplantation. In addition, Dr. Pace highlighted the large capital costs of the robotic platform and steep learning curve of an already technically challenging operation as additional reasons why the robotic platform for kidney transplantation has not gained immediate uptake by high volume programs.

Dr. Breda made equally compelling arguments to the audience by outlining the clear and safe steps of migrating to a robotic platform done by the European Robotic Urology Section of the European Association of Urology. Multicenter, prospective data from 8 European centers show that excellent short-term and 1-year graft outcomes can be achieved with relatively quick learning curves and minimal Clavien-Dindo Grade 1–3 complications using the robotic platform. In addition, novel means of applying regional hypothermia to the graft during the anastomosis, the ability to tackle multivessel reconstruction with excellent magnification and the added benefit of improved wound complication rates in obese transplant recipients makes the robotic approach a feasible candidate at least in experienced hands. With recent reports on the use of robot-assisted transplantation from kidneys obtained from deceased donors and the availability of several hands-on courses in robotic kidney transplantation, this technique has the potential to be implemented by an increasing number of transplant programs globally.

Despite the fruitful discussion including audience participation, many questions remain unanswered and require further debate with topics surrounding justification of additional cost of the use of the robotic platform, the impact of robot training on transplant fellowships, and how to adequately manage both intraoperative and postoperative complications associated with robot-assisted transplantation, to include a few. Overall, the topic of robot-assisted renal transplantation will not be resolved quickly. There is remarkable progress being made on the minimally invasive side. However, it will be a complex balance of surgical innovation, education, graft outcomes and overall costs that will ultimately determine its utility in organ transplantation. We hope that these important topics will continue to be debated and that teams such as Dr. Breda's will keep pushing the boundaries and keep urologists on a strong footing in transplantation. ◆

# The 19th International Prostate Forum at the 2020 Virtual AUA Meeting

**John W. Davis, MD, FACS**
Houston, Texas

**Neal D. Shore, MD, FACS**
Myrtle Beach, South Carolina

The International Prostate Forum (IPF) meets annually at the AUA for a 7-hour format and covers a broad range of diagnostic and therapeutic advances in prostate cancer with an international and multidisciplinary faculty. The group also rotates through collaborative meetings in Turkey and Japan in longer formats that include abstract presentations and benign prostatic hyperplasia (BPH) topics.

For the AUA 2020 virtual meeting highlights we featured 3 of our expert faculty invited for our ongoing AUA–IPF segment described as "Best Of…," which coincides with the AUA meeting location–in this case, "Best of the Mid-Atlantic." The cohosts were John W. Davis, MD from Houston, Texas and Neal D. Shore, MD from Myrtle Beach, South Carolina (see fig. 1 for group Zoom shot).

Dr. James Gulley, a medical oncologist from the National Cancer Institute (NCI), gave a review on genomic testing in prostate cancers entitled "Why Precision Matters." Although many urologists treating localized prostate cancer may have experience with prognostic biomarkers in tissues specimens (Prolaris, Oncotype Dx, Decipher etc), Dr. Gulley reviewed the more precise category of predictive biomarkers in advanced prostate cancer whereby predictive biomarkers have a treatment response effect. Key categories of testing presented (incidence and overlap) included deficiencies in homologous recombination, mismatch repair genes and tumor suppressor genes.

A summary of these predictive biomarkers, how often they are identified and their potential therapeutic overall response rates (ORR) can be seen in figure 2. The mutations are not present in the majority of patients with advanced prostate cancer. However, in these identified patients treatment responses may be multifold more effective when paired with the correct systemic therapy. The review of the PROfound trial for homologous recombination repair gene mutations in patients receiving Olaparib, a novel poly ADP ribose polymerase inhibitor (PARPi), was a highlight of his presentation. In addition, he showed promising early NCI data on the experience with adding PDL-1 inhibitors in BRCA-2 mutations. Further experience is gaining for adding immunotherapy to other patients selected with specific gene alterations.

Dr. Ken Pienta, a medical oncologist from Johns Hopkins/Brady Urological Institute, presented on the topic of prostate specific membrane antigen (PSMA) radioligand therapy. PSMA-positron emission tomography (PET) imaging has been available in a modest number of countries for several years but remains unapproved in the U.S. The sensitivity appears unlike any existing PET tracers in prostate cancer. Dr. Pienta introduced his talk with a summary of 5 distinct questions arising from early experience as follows.

1. Can preoperative staging in high risk be improved?
2. Can recurrent biochemical disease be localized?
3. Can we guide focal therapy at oligometastatic disease?
4. Can we image response to therapy?
5. Can we use PSMA targeted imaging to select patients who would benefit from therapy or "theranostics"?

Theranostics with PSMA-gallium PET have used a novel radiotracer called $^{177}$Lutecium-PSMA. Dr. Gulley presented patient cases of extraordinary response. Early trials have been reported but with the caveats of no control population and significant difference in taxane naïve patients (median 27 months survival) compared to taxane treated patients (median 10.7 months survival). Dr. Pienta then presented his team's meta-analysis on the published experience with the key conclusions that about 40% of patients will have a greater than 50% decrease in prostate specific antigen (PSA), about 70% will have any response in PSA and high grade toxicity (anemia or xerostomia) is less than 5%. Figure 3 shows his take home messages and a key study to look for in 2021.

Dr. Peter Pinto, a urologist at the National Cancer Institute, presented "Current Indispensable Role of MRI to Improve the Diagnosis of Prostate Cancer." As a quick introduction figure 4 shows a summary of indications for multiparametric magnetic resonance imaging (mpMRI) including prior negative biopsy, no prior biopsy, active surveillance and staging. Dr. Pinto summarized these similar key studies as establishing the role of mpMRI and fusion biopsy as part of new standard of care compared to the prior era of 12-core transrectal

▼ Continued on page 25

**Figure 1**. Virtual International Prostate Forum faculty, with Drs. John W. Davis (cohost, top left), Neal D. Shore (cohost, top center), James Gulley (speaker, top right), Ken Pienta (speaker, bottom left) and Peter Pinto (speaker, bottom right).

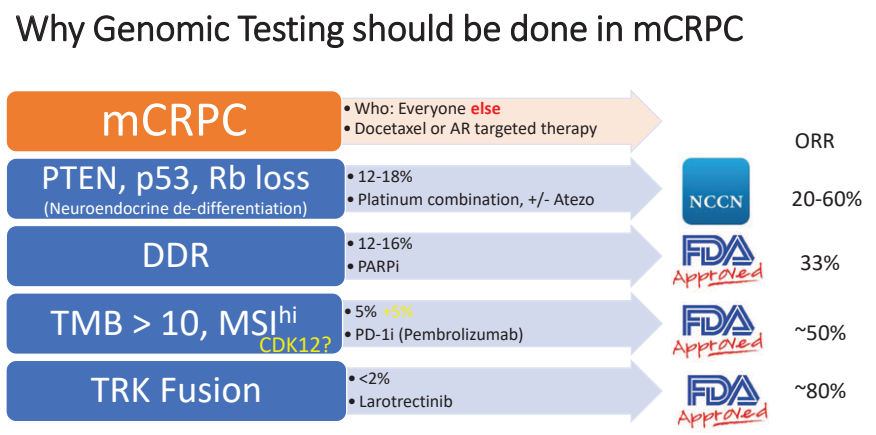


**Figure 2**. Dr. Gulley's summary slide, "Why Precision Matters." *mCRPC*, metastatic castration resistant prostate cancer; *AR*, androgen receptor; *PTEN*, phosphatase and tensin homolog; *DDR*, DNA damage response; *TMB*, tumor mutation burden; *CDK12*, cyclindependent kinase 12; *MSI$^{hi}$*, microsatellite instability – high; *TRK*, tropomyosin receptor kinase.

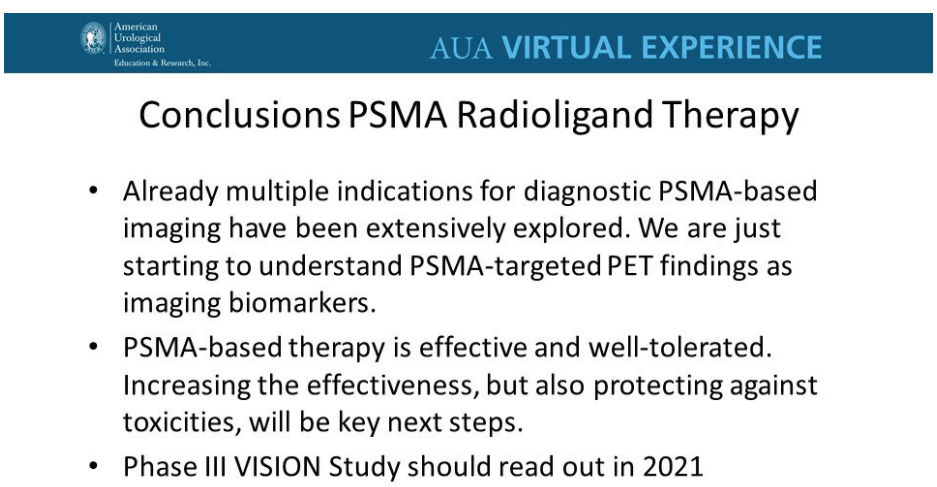


**Figure 3**. Dr. Pienta's summary slide on PSMA radioligand therapy.

## IPF at Virtual AUA2020

▼ Continued from page 24

prostate biopsy (TRUS12). Up to now it is clear from these studies that mpMRI with fusion biopsy increases the detection of high grade cancer by 30% range and decreases detection of low grade cancers by 17%.

The focus of his talk then centered upon his team's recent publication in the *New England Journal of Medicine* that posed the question, do we still need to do the TRUS12 systematic cores if targeting is more accurate?[1] Their series of several thousand fusion biopsies with linked radical prostatectomy pathology in 404 was presented in multiple ways, including incidence of upgrading Gleason grade (GG) 1 to GG2 vs GG3 or higher and risks of downgrading. Then the series was subdivided by targeted biopsies alone, TRUS12 alone and the combination. The key findings included the fact that if TRUS12 were omitted 8.8% of GG3 or higher would be missed, and he suggested that the doctor–patient discussions could decide if that risk was meaningful or not. The next key point was the dramatic reduction in overall GG3 or higher upgrading going from systematic only (30%) to the combination at 6.7%. The key significance of the accuracy improvement is that if a patient is selected for any treatment or any trial the doctor and patient have a better understanding of the true grade and biology of the tumor present. Figure 5 shows his concluding slide.

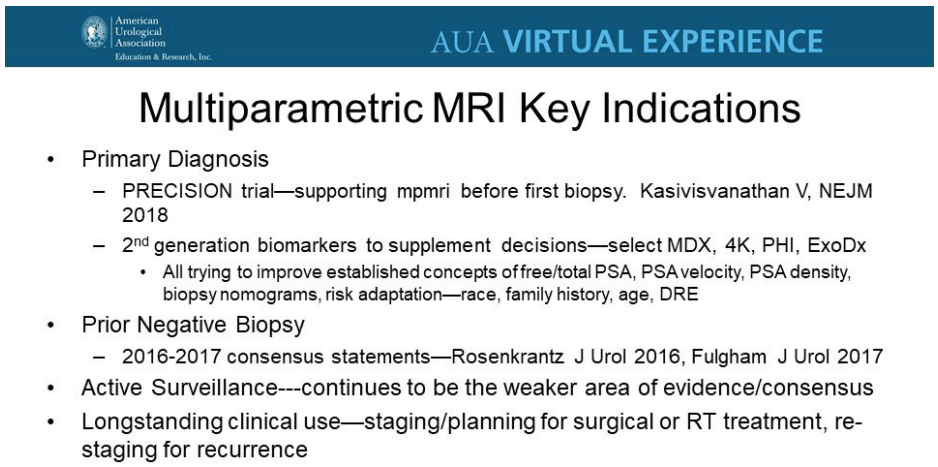


**Figure 4.** Summary of common indications for multiparametric MRI, key references and complementary use with biomarkers and predictors of prostate cancer.

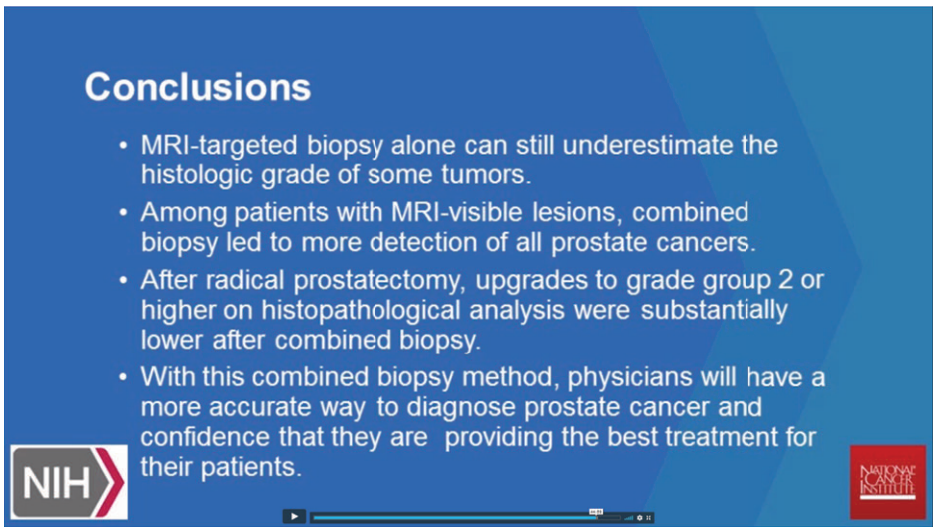


**Figure 5.** Dr. Pinto's summary slide on invaluable nature of multiparametric MRI in accurate prostate cancer diagnosis and therapy strategies.

For our wrap up let me remind our colleagues that this program is available for streaming and CME credit through the AUA University as part of the Saturday AUA virtual 2020 program (https://auau.auanet.org/content/aua-live-saturday-2020). While we prepare for another exciting IPF program for 2021 please also note that the Turkish organizers in our group led by Dr. Erdem Canda will hold a virtual meeting of the IPF December 12–13, 2020 where we will complete the remaining presentations from the 2020 IPF agenda as well as some additions on BPH surgery. The information can be accessed at www.ipf2020.org. We are very appreciative to the AUA Leadership Team for this opportunity to bring you these educational highlights from our featured speakers. ◆

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# SUO 21st Annual Meeting: Extraordinary Opportunities for Discovery

**Michael Cookson, MD**
**President, Society of Urologic Oncology**
Oklahoma City, Oklahoma

The Society of Urologic Oncology (SUO) looks forward to hosting a dynamic annual meeting each year as much as many of you enjoy attending. Our meeting is more than just a chance to catch up on the latest scientific breakthroughs–it is a chance to catch up with colleagues and old friends, and to create new collaboration opportunities and partnerships. Even though we will not meet in Dallas the SUO is working hard to make sure this year is no different.

Our program chairs, board members and staff are planning an exceptional virtual conference experience for all. The SUO Annual Meeting platform will provide ample opportunities to connect via instant messaging and private video conferencing among registrants, and expand on the content presented with dedicated facetime with our knowledgeable speakers and other leaders in the field. We are also looking forward to the opportunity to actually grow attendance as the meeting will be available live to a global audience for the first time.

We are excited to bring you this reimagined experience, and we encourage you to block off **December 3–5** on your calendar as if you were attending in person.

Each day will focus on specific topics so that attendees can better organize their schedules according to their interests. Lectures in prostate and testicular cancer will kick off the meeting on Thursday, December 3. The kidney cancer and health services sessions will follow on Friday, December 4. The meeting will conclude on Saturday, December 5 with the bladder cancer sessions.

Additionally, we have included more opportunities for our abstract submitters to present their work to the audience. The program committee will select the best abstracts in each submission category to be presented during a live, moderated poster session.

We acknowledge the key role this meeting plays for fellows and residents, and so we also ask that Fellowship and residency programs consider blocking time that week to ensure the participation of our trainees. The popular SUO/Young Urologic Oncologists (YUO) Symposium on Clinical Research & Clinical Trials will return on Wednesday, December 2. This course seeks to ensure that each fellow has the tools required to quickly engage in clinical trials upon graduation and to facilitate engagement in the SUO Clinical Trials Consortium. It also serves as a primer for urologists interested in becoming more involved in clinical trials no matter their career stage.

The YUO program is also scheduled for Wednesday evening with a focus on coaching and professional development. Our newly implemented subsection, Women in Urologic Oncology, will also hold their annual networking reception online on Saturday, December 5.

We are also honored to announce Dr. Eila Skinner from Stanford University as this year's Huggins Award Recipient. Each year the Huggins Award is given in recognition of a major contribution

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## SUO 21st Annual Meeting

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and/or lifetime achievement in research and/or clinical practice that has contributed to the progress in the treatment for patients with genitourinary neoplasms. Dr. Skinner is the first woman to receive this award.

The SUO has also instituted a new award dedicated to mentorship, the Joseph A. Smith Jr. Mentorship Lecture, with Dr. Smith as the first recipient.

Finally, we are waiving the registration fee for SUO members not interested in earning continuing medical education credit to show our dedication to you in this difficult time. Let's all make a commitment now to attend and participate to make this meeting the best one we attend this year.

We know that many aspects of trainee education have been disrupted from the COVID-19 pandemic, some programs more than others. The reasons are well-known, with hospital system wide constraints, clinical reassignments, mandated surgical case prioritization and even personal health related factors, among others. The SUO's mission has included supporting our fellow trainees and fellowship programs as much as possible. To that end the Young Urologic Oncologists section of the SUO has launched a webinar series this fall in order to fill some of the didactic gaps programs may be experiencing. The series consists of 2 1-hour lectures of oncologic and nononcologic topics every other Monday at 7:00 p.m. Eastern, running from mid-September through December. We are excited to include such speakers as Drs. David Penson, Kirsten Greene, Stacey Loeb, Matthew Cooperberg, Brant Thrasher and many more to speak on state-of-the-art clinical topics as well as career and professional development.

Additionally, the YUO will be hosting a virtual overview of the SUO Fellowship Program in November, where faculty from the various accredited institutions will provide explanations on the clinical, didactic, research and multidisciplinary components of the program. Interested residents and physicians will then have time to meet with our program directors, faculty and current fellows to discuss these aspects in depth, and obtain advice for the upcoming Match cycle. More information on this broadcast will be made available later this fall. ◆

# Development and Validation of a Urethral Stricture Classification System

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**Justin Drobish, MD**
**Katherine Cotter, MD**
**Amy Hahn**
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**Nejd Alsikafi, MD**
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**Benjamin Breyer, MD, MAS**
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**Joshua Broghammer, MD**
Kansas City, Kansas

**Jill Buckley, MD**
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**Sean Elliott, MD, MS**
Minneapolis, Minnesota

**Jeremy Myers, MD**
Salt Lake City, Utah

**Andrew Peterson, MD, MPH**
**Keith Rourke, MD**
Edmonton, Alberta, Canada

**Thomas Smith III, MD**
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**Alex Vanni, MD**
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**Bryan Voelzke, MD, MS**
Spokane, Washington

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New York, New York

Male urethral stricture disease is a disease process with a complex pathophysiology yet to be fully understood in the majority of stricture types. The current lack of a urethral stricture classification system impairs clinical communication, inhibits our understanding of surgical outcomes and impedes research efforts. In an effort to remedy these current shortcomings we sought to develop and validate a male anterior urethral stricture classification system. The classification system is based on readily available clinical information including patient history, physical exam and a retrograde urethrogram (RUG) with an emphasis on being easy to use and having a high interrater reliability (ie different urologists classifying a given stricture the same).

The classification nomenclature is based on 3 readily available clinical variables–stricture length (L), stricture segment (S) and stricture etiology (E)–known to influence urethral stricture treatment choice and outcomes.[1,2,3] Thus, the LSE-urethral stricture classification system was devised as shown in figure 1. Each variable was further subdivided in a manner believed to reflect stricture complexity or surgical management. Length was subdivided based on common surgical management. For example, strictures less than 2 cm are commonly managed with an excisional procedure, strictures 2 to 7 cm can be managed with a single graft and strictures longer than 7 cm generally require a second graft. Urethral segments were divided into bulbar–S1, pendulous–S2 and panurethral strictures–S3 (defined now as a single stricture involving the meatal/fossa, penile and bulbar urethral components) with additional subdivision reflective of the anatomical implications on surgical repair.

A visual representation of each urethral segment definition is shown in figure 2. Etiology divisions were arranged in order of presumed/accepted increasing complexity. For example, straddle injuries (E1) are generally short segments with healthy surrounding tissue compared with lichen sclerosus (E6) strictures which can progress in length and severity markedly increasing the complexity of repair. Additional modifiers for obliterated urethral lumen, multiple stricture segments and extension into the posterior urethra were included.

The LSE definitions were validated in a multistep process. Urethral stricture clinical vignettes detailing clinical history, physical examination findings and a RUG were distributed to 20 reviewers (reconstructive urologists and fellows). Each reviewer applied a LSE classification to each vignette. The survey results were aggregated and

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**TURNS LSE Anterior Urethral Stricture Classification System**

| | |
|---|---|
| **L – Length*** | |
| 1 | ≤ 2cm |
| 2 | > 2cm & ≤ 7cm |
| 3 | > 7 cm |
| **S – Urethra Segment**** | |
| 1 | **Bulbar Urethra** |
| 1a | Bulbar Urethral Stricture without Distal Bulbar Urethra involvement. |
| 1b | Bulbar Urethral Stricture Involving the Distal Bulbar Urethra. |
| 2 | **Penile Urethra** |
| 2a | Stricture involving both bulbar and penile urethral segments without involvement of the fossa navicularis and/or urethral meatus. |
| 2b | Stricture isolated to the penile urethra without fossa navicularis or meatal involvement. |
| 2c | Stricture isolated to the penile urethra with fossa navicularis and/or meatal involvement. |
| 2d | Stricture isolated to the fossa navicularis and/or urethral meatus. |
| 3 | Stricture involving the meatus/fossa, penile urethra and bulbar urethra (i.e. pan-urethral stricture). |
| *S – Modifiers* | |
| x | Portion(s) of the Stricture with Obliterated Lumen (e.g. S1ax, S2ax) |
| m | Separate strictures involving two or more distinct areas of the anterior urethra (managed with separate urethroplasty techniques). (e.g. Sm1a and Sm2d) |
| p | Extension of stricture into posterior urethra (non-PFUDD; e.g. S1ap), or isolated non-PFUDD posterior urethral stricture (e.g. Sp) |
| **E – Etiology ***** | |
| 1 | External Trauma (e.g. known straddle injury) |
| 2 | Idiopathic/Unknown Etiology |
| 3 | Iatrogenic |
| 3a | Internal Trauma (e.g. post TURP/TURBT stricture) |
| 3b | Recurrent Urethral Stricture in Prior Urethroplasty Segment (including penetrating injury healing with stricture +/ - prior repair; excluding hypospadias repairs (E5)) |
| 3c | Radiation Induced Urethral Stricture |
| 4 | Infectious/Inflammatory (e.g. post-gonococcal) |
| 5 | Stricture in Segment of Prior Hypospadias Repair |
| 6 | Lichen Sclerosus |

* Total length of the diseased urethra being managed with a single urethroplasty technique. If an m modifier is utilized, two L variable values will be listed.

** If multiple strictures are radiographically isolated but are managed with a single technique, classify as a single stricture. If the strictures are managed separately (e.g. anastomotic repair for bulbar stricture, onlay for penile repair) then the m modifier should be utilized

*** If multiple etiologies suspected/known, stage with highest numbered etiology.

**Figure 1.** LSE Anterior Urethral Stricture Classification System.

## Urethral Stricture Classification System

▼ Continued from page 26

analyzed for interrater reliability using Cohen's Kappa and Light's Kappa. An a priori kappa value of 0.7 or greater (indicating substantial interrater agreement) was chosen as the threshold needed to ensure sufficient agreement. Reviewer feedback and analysis of vignettes with poor agreement were used to revise the classification system in an iterative fashion (3 rounds). The final LSE definitions were agreed upon at an in-person meeting of the Trauma and Urologic Reconstruction Network of Surgeons.

The overall kappa for the LSE urethral stricture classification system was 0.79 indicating substantial interrater agreement (kappa value of 0.6 or greater = substantial agreement). The final kappa for each LSE component was L=0.76, S=0.7 and E=0.93, again indicating substantial agreement for each component.

The LSE anterior urethral stricture classification system provides urologists who treat urethral stricture disease a means to classify this challenging disease process and to better communicate with each other. We demonstrated that urologists were readily able to learn and implement the LSE urethral stricture classification system with excellent agreement. Importantly, improved classification affords urologists the ability to study and research the treatment of specific urethral stricture subtypes in a more apples-to-apples fashion and truly advance the field.

Our hope is that widespread adoption of the LSE urethral stricture classification system will serve urologists in a manner analogous to the TNM tumor stage such that upon reading L1S1bE1 a urologist will create a mental image of a short segment bulbar urethral stricture resulting from trauma and begin to formulate a surgical plan. The complete results of our efforts are published and available for review in the September 2020 volume of *Urology*.[4]

*AUA 2020 Virtual Science Best Poster winner.* ◆

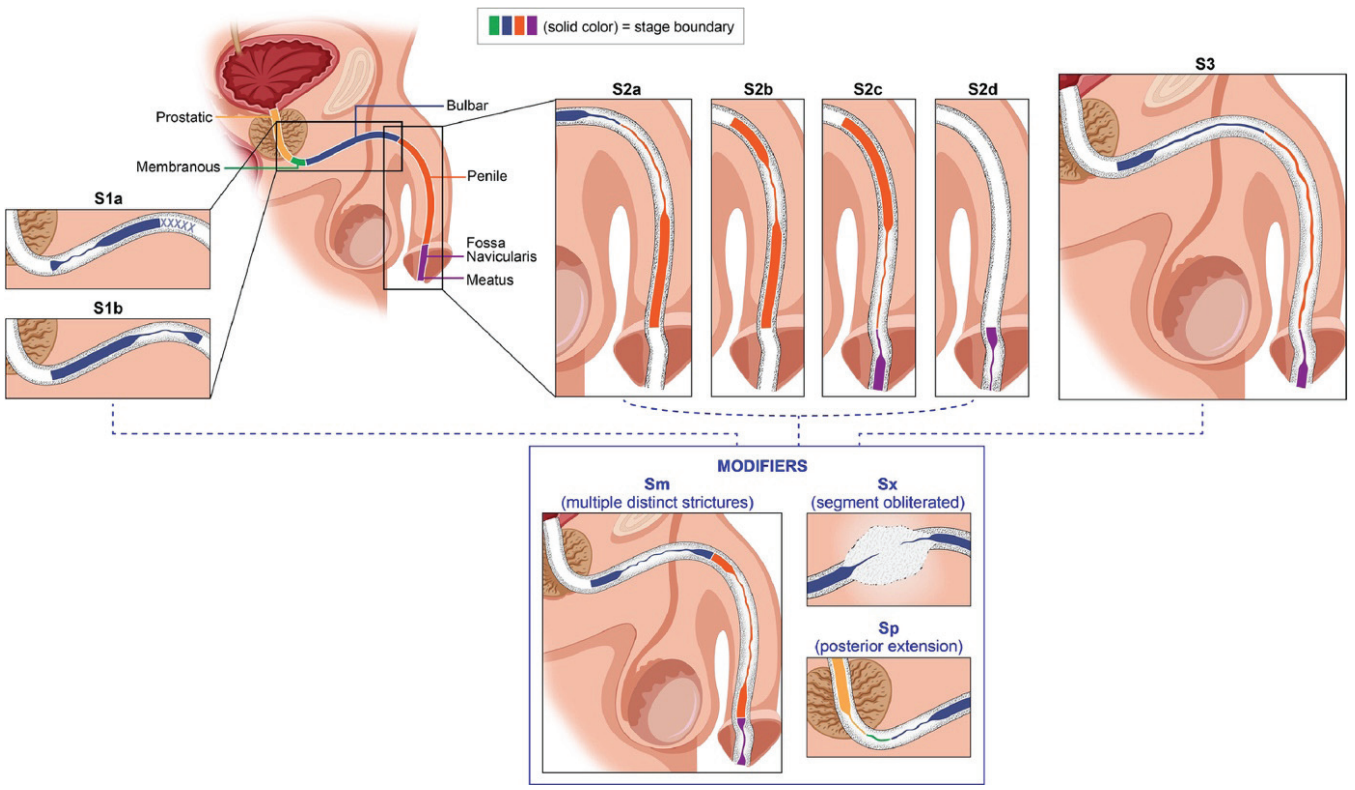


**Figure 2.** LSE classification segment (*S*) variables with modifiers.

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3. Barbagli G, Montorsi F and Balo S: Treatments of 1242 bulbar urethral strictures: multivariable statistical analysis of results. World J Urol 2019; **37**: 1165.
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# Spatial Distribution and Differential Localization of Protein Matrix in Kidney Stones

**Yutaro Tanaka, MD**
Nagoya, Japan

The question of whether it is possible to avoid the invasive treatment of kidney stones if the stone growth itself can be stopped at an early stage is the starting point of our research. Kidney stone is a common disease that affects approximately 20% of the global population at an increasing rate of prevalence.[1] Furthermore, the recurrence rate of kidney stone is approximately 10% a year and 30% to 50% every 5 years. Once a stone is formed in the kidney, regardless of its size it continues to grow and eventually requires an invasive treatment unless excreted via urine.

In recent times, due to advancements in technology and equipment, invasive procedures can be performed with minimum invasiveness. However, serious complications cannot be avoided. These facts suggest that emphasis must be placed on preventing the growth of kidney stones. Therefore, elucidating the mechanism of kidney stone formation is essential for the development of an effective therapy to prevent their growth.

Kidney stones are composed 90% of mineral components and a few percent of protein matrix. Kidney stone formation is a multistep process comprised of nucleation, growth, aggregation and concretion of the crystals which requires mineral components and the protein matrix. These processes are recorded inside the fine structure of kidney stone as the "history" of stone formation.[2] However, the topographic relationship between mineral components and protein matrix remain uninvestigated and might be crucial for the stone formation.

Many studies have been conducted to elucidate the mechanism of stone formation using the latest techniques for structural analysis such as infrared spectroscopy, microcomputed tomography and electron microscopy.[3] However, most of these studies have been focused on understanding the role of mineral components in kidney stone formation. On the other hand, elucidating the role of the protein matrix in stone formation is important since it is known to have a great influence on the stone formation process. There are more than 100 types of protein matrices identified in kidney stones.

As a representative of morphological study Chien et al identified the distribution of osteopontin (OPN) in decalcified and dehydrated kidney stone samples using electron microscopy.[4] Since then there have been a few reports on the distribution of specific proteins in kidney stones. Analyzing the fine structure of kidney stones that maintains the spatial relationship of the mineral phase and protein composites allows us to identify the interaction between them and the role of matrix proteins in the kidney stone formation processes.

In this study we analyzed 3 calcium binding proteins, namely OPN, renal prothrombin fragment 1 (RPTF-1) and calgranulin A (Cal-A), that are commonly present in kidney stones and are known to play a significant role in the process of stone formation. First,

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## Protein Matrix in Kidney Stones

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we conducted a detailed structural analysis using stone thin sections that maintained the morphological changes. Thereafter, we identified the calcium oxalate crystals in different phases and their spatial structures using bipolarized optical microscopy and Fourier transform infrared spectroscopy. In addition, the protein distribution of the samples was visualized by multicolor immunofluorescence (Multi-IF) staining.

Kidney stones are known to consist of 3 typical crystal textures, namely idiomorphic calcium oxalate dihydrate (COD) crystals (Type 1), irregular calcium oxalate monohydrate (COM) crystals (Type 2) and concentrically laminated COM crystals (Type 3). We distinguished the 3 types of crystal textures and visualized the presence of the 3 proteins (OPN, RPTF-1 and Cal-A) by Multi-IF staining. Figure 1 shows Type 1 in which OPN was partially visualized along the tips of the COD crystal edge (white arrow), RPTF-1 was visualized in layers parallel to the COD crystal edge

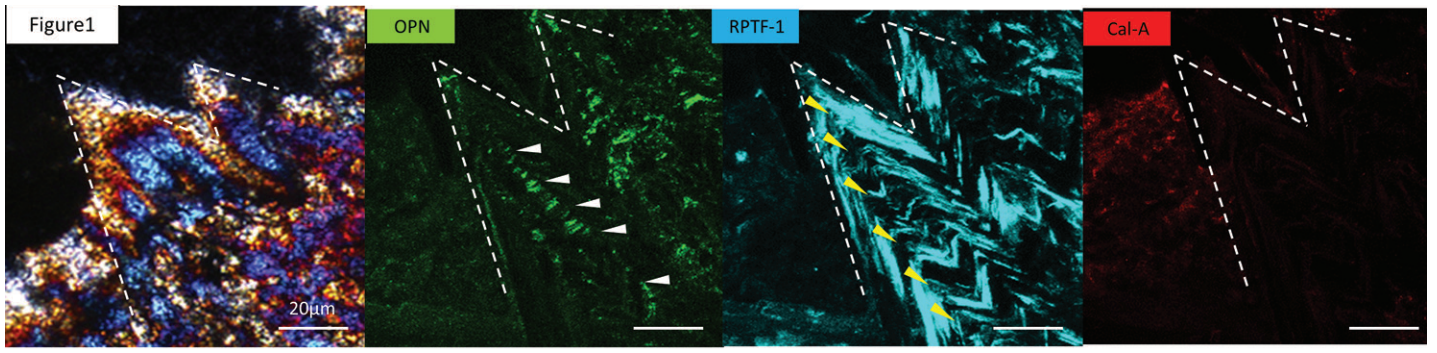



**Figure 1.**

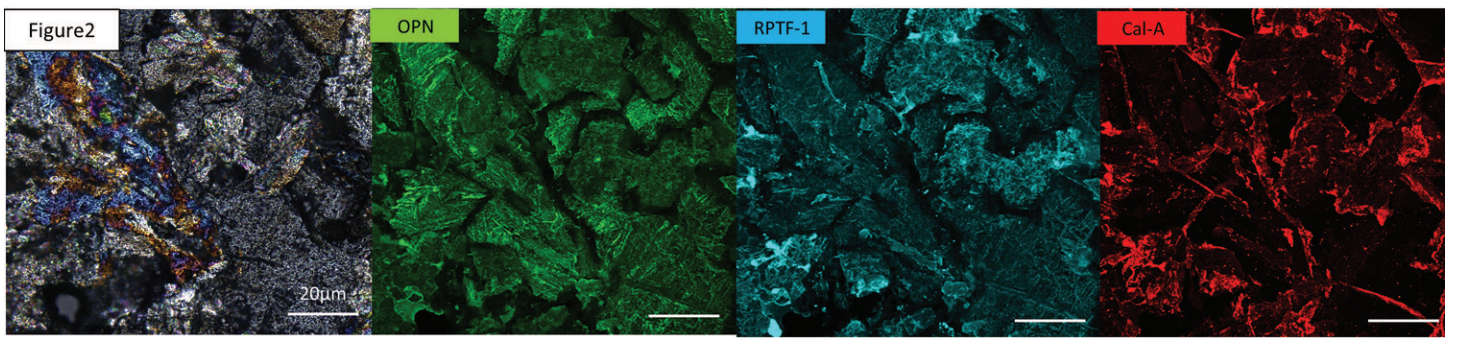



**Figure 2.**

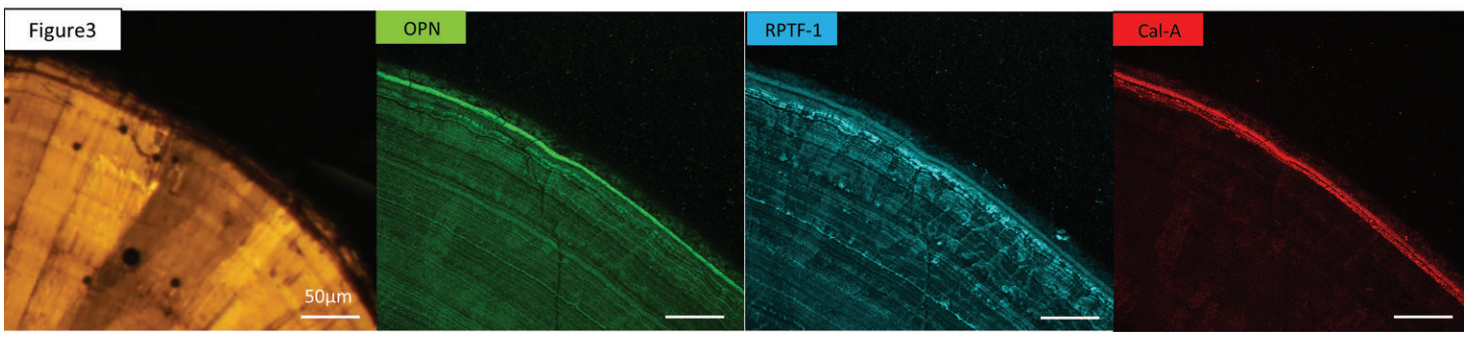



**Figure 3.**

(yellow arrow) and Cal-A was not visualized within the COD crystal. Figure 2 shows Type 2 in which OPN and RPTF-1 were observed in the crystals and the staining was observed in a mosaic pattern. In contrast, Cal-A was not observed within the crystals but only at the grainy boundaries between the crystals. Finally, figure 3 shows Type 3 in which OPN and RPTF-1 were observed in layers throughout the concentrically laminated COM crystals at intervals of several concentric rings. In contrast, Cal-A was observed faintly in irregular layers.

We visualized the distribution of 3 different proteins in COM and COD crystals and discovered their spatial distribution and the differential localization of the protein matrix in kidney stones. The different distribution patterns of proteins might imply the specific function of each protein based on their physicochemical and/or biological properties during the stone formation. However, we need further discussion on why the 3 proteins showed different distribution patterns or how these 3 proteins play a role during stone formation.

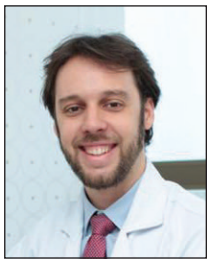
Therefore, further analysis is needed to confirm the protein distribution in kidney stones. The identification of specific proteins in kidney stones using this new method provides insights for understanding the association of proteins with different mineral phases in these pathological samples and elucidating the stone formation process, which could further lead to the development of effective therapies to prevent stone growth.

*AUA 2020 Virtual Science Best Poster winner.* ◆

1. Yasui T, Okada A, Hamamoto S et al: Pathophysiology-based treatment of urolithiasis. Int J Urol 2017; **24**: 32.
2. Sivaguru M, Saw J, Williams JC et al: Geobiology reveals how human kidney stones dissolve in vivo. Sci Rep. 2018; **8**: 13731.
3. Castiglione V, Sacre P-Y, Hubert P et al: Raman chemical imaging, a new tool in kidney stone structure analysis: case study and comparison to Fourier transform infrared spectroscopy. PLoS One 2018; **13**: e0201460.
4. Chien YC, Mansouri A, Jiang W et al: Modulation of calcium oxalate dihydrate growth by phosphorylated osteopontin peptides. J Struct Biol 2018; **204**: 131.

# Seminal Vesiculoscopy for Refractory Hematospermia and Ejaculatory Duct Obstruction

**Eduardo P. Miranda, MD, PhD, FECSM**
Fortaleza, Brazil



**Filipe Tenório Lira Neto, MD, Msc**
Recife, Brazil

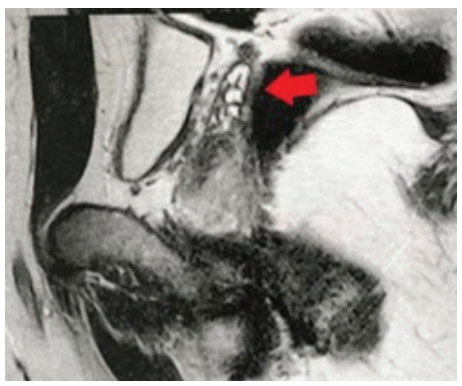
A 44-year-old man presented with a 3-year history of persistent low seminal volume and recurrent episodes of hematospermia. He was married to a 42-year-old wife and complained of primary infertility with unsuccessful attempts to conceive for 10 years. The patient had history gastric bypass surgery for severe obesity 3 years ago. Physical examination was positive for bilateral grade II varicoceles. Digital rectal examination was unremarkable with nontender prostate and nonpalpable seminal vesicles.

Semen analysis confirmed decreased semen volume (0.5 ml, reference greater than 1.5 ml), hematospermia (3,700 red blood cells, no reference), decreased total sperm count (300,000 sperm, reference greater than 39 million), decreased progressive motility (20%, reference 32%) and borderline morphology using the strict Kruger criteria (4%, reference greater than 4%). Hormonal assessment was within normal limits. Contrast enhanced pelvic magnetic resonance imaging revealed dilation of the right seminal vesicle and right ejaculatory duct with no signs of inflammatory, neoplastic or cystic lesions within the prostate (fig. 1).

At this point the patient was informed of a likely diagnosis of partial ejaculatory duct obstruction. In this scenario endoscopic seminal vesiculoscopy was offered as a diagnostic and potential treatment option for improvement of hematospermia episodes and semen parameters. It was also explained that microsurgical varicocelectomy would probably be required in the future to improve his spermatogenesis.

Urethroscopy was initially performed using a 6Fr ureteroscope. Catheterization of the ejaculatory duct orifices with a hydrophilic guidewire was unsuccessful through the verumontanum, and then the internal cavity of the prostate utriculum was accessed. As the orifices were not identified unroofing of the verumontanum with a 26Fr resectoscope was performed and drainage of dark fluid was observed coming from the right ejaculatory duct. This maneuver allowed the guidewire to be inserted and the ureteroscope was progressed in the right seminal vesicle using intermittent low pressure irrigation and gentle alternate rotation (fig. 2). Several small stones and amorphous material were flushed out and the final revision demonstrated absence of residues (fig. 3). The procedure was repeated on the left side, and a milky fluid was drained after guidewire insertion without significant findings during vesiculoscopy. The final endoscopic evaluation revealed an unroofed prostatic utriculum and the dilated ejaculatory duct orifices at the 2 and 10 o'clock positions (fig. 4). No significant bleeding was observed, digital rectal examination was negative for blood and an 18Fr urethral Foley catheter was left in place overnight.

A



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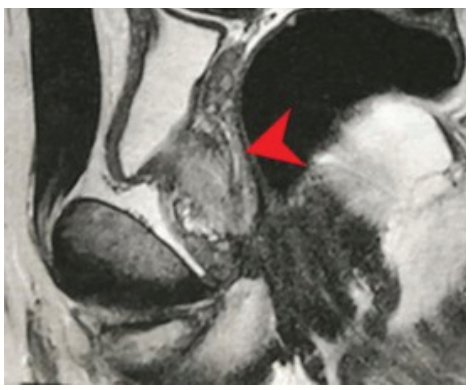

**Figure 1.** *A*, dilated right seminal vesicle (red arrow). *B*, dilated right ejaculatory duct (red arrowhead).

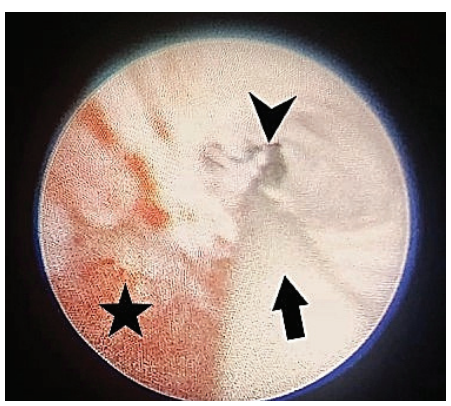

**Figure 2.** Unroofed prostate utriculum cavity (star), guidewire (arrow) and right ejaculatory duct opening (arrowhead).

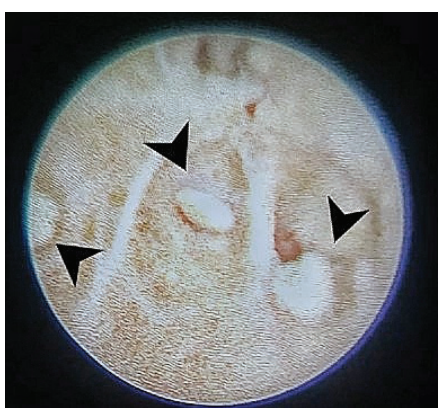

**Figure 3.** Small calculi in right seminal vesicle (arrowheads).

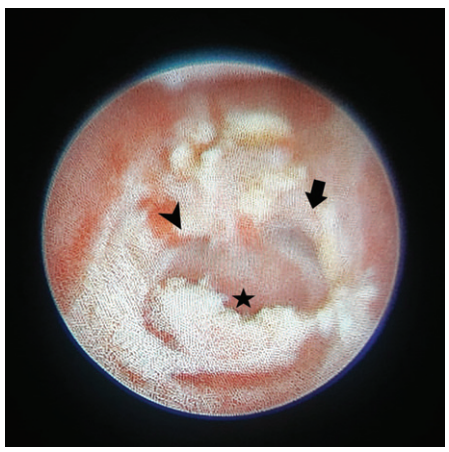

**Figure 4.** Unroofed prostate utriculum cavity (star), right ejaculatory duct opening (arrow) and left ejaculatory duct opening (arrowhead).

The patient was discharged the following day and was counseled to resume sexual activity as soon as possible to maintain ejaculatory duct patency. A new semen analysis was performed 1 month after the procedure and revealed normal ejaculate volume (2.0 ml), no red blood cells, an increase in the total sperm count to 1,000,000 per ejaculate, improved morphology (10%) and unchanged progressive motility (20%). The patient reported a subjective feeling of increased ejaculatory volume and had no complaints of hematospermia, pain or sexual dysfunction at a 6-month followup visit.

Ejaculatory duct obstruction is a rare condition identified in up to 5% of infertile men. Patients with ejaculatory duct obstruction may present with low seminal volume, oligoasthenospermia or azoospermia, hematospermia, painful ejaculation, chronic pelvic pain or male infertility. This is usually a challenging diagnosis as traditional diagnostic workup with semen analysis and imaging studies have limited accuracy.[1,2] While transurethral resection of the ejaculatory ducts (TURED) has good efficacy for distal duct obstruction, results for proximal obstruction are less convincing. In addition, TURED might lead to severe complications such as rectal injury and urinary incontinence.

Recently, the use of high quality endourological devices has allowed the development of seminal vesiculoscopy, which has become an alternative to TURED in the management of several conditions in the prostate, ejaculatory ducts and seminal vesicles.[3] It requires a profound understanding of the male pelvic anatomy associated with the endoscopic ability to recognize tiny structures and anatomical landmarks. The ejaculatory duct orifices can be accessed through either the utriculum or the urethra directly.

Most cases will require the transutricular approach, which involves using ureteroscopes and guidewires to enter the utricular lumen before catheterizing the orifices. The urethral approach is only possible when the ejaculatory duct ostia are found directly on the urethral surface. Finally, resection of the verumontanum to expose the posterolateral path of the ejaculatory ducts is another alternative. However, this last technique should be applied carefully because it could increase the chance of reflux epididymitis, urinary incontinence and rectal injury.

Several reports have demonstrated that seminal vesiculoscopy appears to be a safe and minimally invasive option for ejaculatory duct obstruction, persistent hematospermia and some cases of pelvic pain. The procedure is feasible in most patients, and outcomes are promising with resolution of hematospermia ranging from 78% to 98% and recurrence rates as low as 10%.[1,4,5] Although pelvic pain or ejaculation related pain could be improved after seminal vesiculoscopy,[5,6] up

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## Seminal Vesiculoscopy

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to 30% of the patients may develop perineal pain or discomfort postoperatively, which tend to be mild and temporary.[4] Postoperative epididymitis seems to be rare and could be avoided with limited pressure during irrigation. No other major complications have been described in the literature. ◆


1. Xing C, Zhou X, Xin L et al: Prospective trial comparing transrectal ultrasonography and transurethral seminal vesiculoscopy for persistent hematospermia. Int J Urol 2012; **19**: 437.
2. Han CH, Liang Q, Dong BZ et al: The transurethral seminal vesiculoscopy in the diagnosis and treatment of the seminal vesicle disease. Cell Biochem Biophys 2013; **66**: 851.
3. Lira FTN, Bach PV, Miranda EP et al: Management of ejaculatory duct obstruction by seminal vesiculoscopy: case report and literature review. JBRA Assist Reprod 2020; **24**: 382.
4. Han WK, Lee SR, Rha KH et al: Transutricular seminal vesiculoscopy in hematospermia: technical considerations and outcomes. Urology 2009; **73**: 1377.
5. Liu B, Li J, Li P et al: Transurethral seminal vesiculoscopy in the diagnosis and treatment of intractable seminal vesiculitis. J Int Med Res 2014; **42**: 236.
6. Kang PM, Seo WI, Yoon JH et al: Transutricular seminal vesiculoscopy in the management of symptomatic midline cyst of the prostate. World J Urol 2016; **34**: 985.


# RADIOLOGY *Corner*

**Joseph N. Sarcona, MD**

**Ivan Grunberger, MD**

New York, New York

A urology consult for possible bladder perforation in a patient with no history of trauma was called. A 72-year-old female with past medical history of diabetes mellitus, hypertension, glaucoma, chronic hepatitis C (treated with Harvoni®) and recent COVID-19 pneumonia presented to the emergency department in critical condition with 2 days of nonbloody, nonbilious emesis and lethargy without any history of trauma. In the emergency room (ER) she was found to be in new onset atrial fibrillation with rapid ventricular rate.

There were multiple lab abnormalities, but notable to the case her blood urea nitrogen was 76 and creatinine was 3.6. Her COVID-19 admission consisted of medical treatment complicated by acute kidney injury without need for intubation. A Foley was placed in the ER with clear/yellow urine return. The ER physician ordered computerized tomography (CT) chest/abdomen/pelvis, which demonstrated a Foley balloon outside of the bladder with a significant amount of pelvic and abdominal free fluid that was concerning for bladder perforation (fig. 1).

When approached with a situation such as this it is important to start with the basics and workup as with any case. Although the patient was unable to provide much history secondary to lethargy, some pertinent positives and negatives were elucidated. Of note, the patient had no trauma and there was no blood at the meatus or in the urine (gross or microscopic). She did not have a history of abdominal or pelvic malignancy but did recently have COVID-19 infection, which is known to have some long-term health sequelae including cardiomyopathy. Her initial CT abdomen showed pelvic ascites that was in the shape of the bladder, which confused the radiologists.

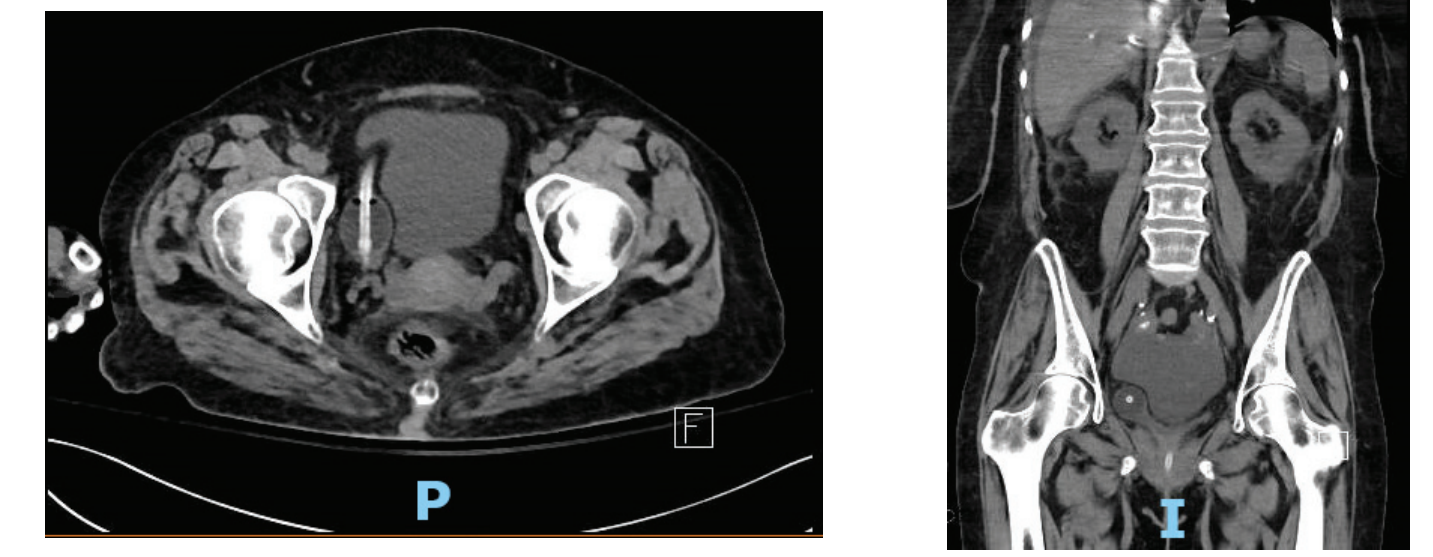


**Figure 1.** CT abdomen (*A*)/pelvis (*B*) showing what appears to be Foley outside of bladder. In retrospect area that appeared to be bladder was pelvic ascites and Foley was inside decompressed bladder pushed to side of pelvis.

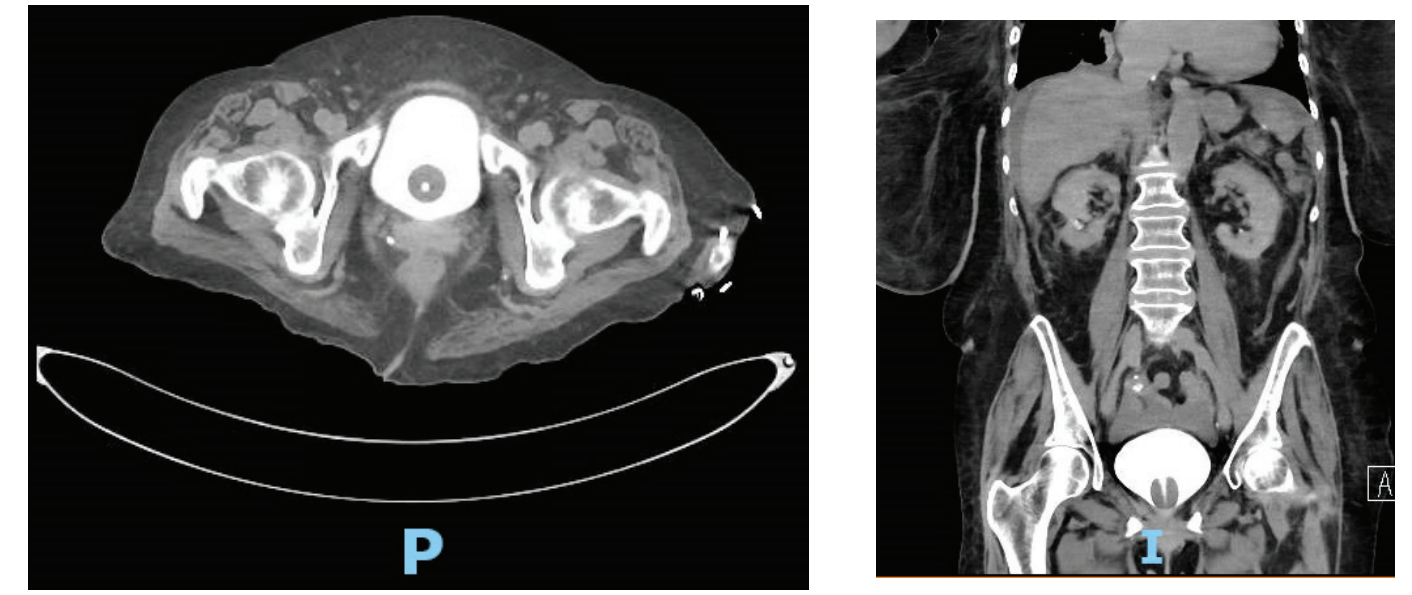


**Figure 2.** *A, B,* CT cystogram showing Foley in place inside normal bladder. Pelvic ascites has been displaced upward into abdominal cavity.

For a bladder injury/rupture AUA guidelines recommend to perform retrograde cystography.[1] A CT cystogram was performed as described in the stress urinary incontinence guidelines, with a precontrast phase to ensure no confusion with previous IV or oral contrast, a contrast filling phase where 350 to 400 cc of dilute omnipaque contrast instilled through the Foley catheter and a postdrainage phase after draining the bladder.[2] Figure 2 presents images of the CT cystogram showing the Foley obviously in the bladder with no extravasation.

The patient ended up having new onset congestive heart failure (CHF), likely a complication of COVID-19, with cardiogenic shock and a large amount of abdominal and pelvic ascites. Differential diagnosis for the imaging included bladder rupture, bladder diverticulum, Foley in place in a normal bladder with abdominal/pelvic ascites from secondary process such as cancer, CHF etc. ◆


1. Morey AF, Brandes S, Dugi DD 3rd et al: Urotrauma: AUA guideline. J Urol 2014; **192**: 327.
2. Gomez RG, Ceballos L, Coburn M et al: Consensus statement on bladder injuries. BJU Int 2004; **94**: 27.

FROM THE *Urology Care Foundation*

# Improving Patient Lives through Crucial Initiatives during National Bladder Health Month

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

November is National Bladder Health Month, a time when the Urology Care Foundation deepens our commitment to raising awareness about the importance of this vital organ and the myriad ways it affects our well-being. Maintaining, improving and building awareness about bladder health patient education and research can improve the lives of those struggling with bladder health issues worldwide.

### Patient Advocacy & Research

This past year along with the AUA we hosted the Patient Advocacy Connections Program. This year's virtual event successfully connected more than 50 participants from 35 urology focused patient advocacy organizations throughout the 3-day series. The program included 2 engaging roundtable discussions. The first addressed health literacy and health equity challenges, and the second focused on effective advocacy communication strategies.

The Patient Advocacy Connections program also featured Advocacy Rounds, a virtual networking event. This interactive event connected participants with key members of our leadership including members of the AUA's Board of Directors, the Public Policy Council, Legislative Affairs Committee, Research Advocacy Committee and more. This year's event had a strong emphasis on bladder health and provided an opportunity for AUA members to learn about our partners and their advocacy areas of interest.

Our work connecting with patient advocacy organizations has driven important opportunities to collaborate on legislative efforts that have and will continue to benefit patients and their loved ones.

The Foundation is committed to funding and advancing research through the generous support of donors like you. We have provided more than $34 million in funding to help nearly 900 of the brightest minds conduct innovative urology research. One day our research may help cure or prevent bladder cancer. As we know, we do this because we understand the cures of tomorrow exist in the lab.

### Bladder Health Patient Education

Educating patients is fundamental to our mission. November represents the cornerstone of our commitment to educating patients and encouraging all patients to talk to their doctor about their bladder health. We are working to make sure those at risk for bladder cancer are aware of the importance of knowing the risk factors. Reliable patient education on bladder health issues has never been more vital in this "Wild West" time of information.

Our library of educational resources are based on the AUA's clinical practice guidelines. Our resources are available in many different types of media and languages. Some of these offerings include:

- Nonmuscle Invasive Bladder Cancer Patient Guide
- Muscle Invasive Bladder Cancer Patient Guide
- Incontinence Patient Guide
- Overactive Bladder-Assessment Tool
- Bladder health facts and stories, and a collection of videos and podcasts

Please make sure to send your patients to UrologyHealth.org/BladderHealth and ensure they receive these trusted resources during this crucial awareness month. We encourage all of you on social media to use the #BladdersMatter hashtag on Twitter, Instagram and Facebook during the month of November! Thank you. ◆

FROM THE *AUA Research Council*

# Standing Urology Study Section Returns to NIH

**Aria F. Olumi, MD**
**Chair, AUA Research Council**
Boston, Massachusetts

Investigator initiated research grants submitted to the National Institutes of Health (NIH) undergo a rigorous review process for consideration of financial support. Grants are initially screened by the Center for Scientific Review (CSR) and assigned to different study sections for scientific merit review and scoring by experts in the field. Expert reviews are submitted from the CSR to the NIH institutes, and the program officers at NIH determine suitability for funding based on the expert panels' reviews and needs for research in specific disease areas. The review process by the panel of external experts is a critical step that helps determine whether a research application is suitable for funding from the federal government.

During the last decade, because of the limited number of research grant applications submitted in functional urological disorders (excluding urological malignancies) reviews have been conducted by a "special emphasis panel," which is an ad hoc assembly of experts in the field as opposed to a panel with a regular membership of experts assigned to a "standing" study section chartered to review a specified scientific area of grant applications. Commonly, because of the fierce competition for federal research dollars and low funding rates applications are not funded after their first submissions but have to be resubmitted to NIH for reevaluation and reconsideration after addressing reviewer concerns with the initial application. Given the ad hoc nature of the special emphasis panel urological researchers have felt that special emphasis panels do not offer the same level of consistency in their reviews from one review cycle to the next. In contrast, standing study sections provide more consistent reviews and may better serve the needs for our urological research community.

Recently, CSR completed a major initiative, ENQUIRE (Evaluating Panel Quality in Review),[1] which involved input from multiple stakeholders with the goal of improving the overall study section structure. As a result, CSR developed the Kidney and Urological Systems Function and Dysfunction (KUFD) standing study section, which is designed to review NIH grant applications that focus on the developmental mechanisms and function of the kidney and urinary tract including the ureters, bladder and urethra, the male genital tract, and the visceral pelvis and pelvic floor musculature.[2] The institution of this standing study section for urology research grants will assure more consistency and better reviews, which will help advance research.

To ensure that urology research applications are evaluated by the most appropriate experts our AUA Research Advocacy Committee, led by Dr. Toby Chai, along with committee member Dr. Wade Bushman, are collaborating with CSR to provide lists of experts in different fields of urology who can be considered for grant reviews. However, to assure fair and educated reviews of urology research applications, when asked to serve it is imperative that our urology experts accept the invitations for grant reviews openly. ◆

1. National Institutes of Health: ENQUIRE (Evaluating Panel Quality in Review). National Institutes of Health 2019. Available at https://public.csr.nih.gov/StudySections/CSREnquire.
2. National Institutes of Health: Kidney and Urological Systems Function and Dysfunction (KUFD). National Institutes of Health 2020. Available at https://public.csr.nih.gov/StudySections/DPPS/DKUS/KUFD.

FROM THE *AUA Secretary*

# Partnering with Specialty Societies

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

Partnerships are important in all aspects of life. The AUA would not be able to advance urology without partnering with the urology community, including urological specialty societies. These partnerships are important to the success and growth of our specialty.

Collaboration between the AUA and specialty societies provides opportunities for society leaders and members to participate and lend their expertise to AUA councils and committees and other activities. The AUA actively participates with societies in the development of clinical guidelines and best practice statements, including partnership and collaboration in joint projects. Societies provide input for the AUA Annual Meeting, Annual Urology Advocacy Summit and educational courses. They also contribute to AUA*News*, developing patient education for the Urology Care Foundation, and podcasts for the AUA and the Foundation.

In addition, these specialty societies help the AUA with CME accreditation, improving urology research and funding endowments, quality projects, data, international programs, public policy and advocacy, and more. The knowledge the specialty societies bring to each of these initiatives ensures all specialties of urology are covered.

The AUA is proud of its ongoing relationships with the Endourological Society, Society of Genitourinary Reconstructive Surgeons (GURS), Society of Academic Urologists (SAU), Sexual Medicine Society of North America (SMSNA), Societies for Pediatric Urology (SPU), Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU), and Society of Urologic Oncology (SUO). Each of these groups interacts with the AUA to bring knowledge, expertise and support to AUA initiatives.

Some recent collaborations between the AUA and societies include:

- Partnering with the **Endourological Society** on quality improvement projects
- **GURS** and the AUA Coding and Reimbursement Committee working on a joint coding project for difficult reconstructive surgeries
- Podcasts about COVID-19 and Residency and Transition from Residency to Fellowship with **SAU**
- Working with **SMSNA** on AUA Guidelines such as Disorders of Ejaculation
- Developing important pediatric urology information for the Urology Care Foundation's quarterly magazine, *UrologyHealth extra*® with **SPU**
- Partnering with **SUFU** on the Hematuria guideline
- Working with **SUO** to engage in the development of a Patient-Centered Outcomes Research Institute (PCORI) grant to support a meeting focused on improving active surveillance

It may sound trite, but the old adage rings true when we say, "Together we are stronger." When we come together collectively to advance urology, we all win. The AUA looks forward to our continued partnerships with urological societies around the world. ◆

FROM THE *Chief Executive Officer*

# Patient Education Resources

**Michael T. Sheppard, CPA, CAE**
Linthicum, Maryland

Nearly 20 years ago the AUA embarked on a journey to develop a comprehensive, online patient education website. UrologyHealth.org was launched in 2002 and in the years since has grown to become the crown jewel of the Urology Care Foundation's compendium of patient education developed by urologists.

At present the Urology Care Foundation offers more than 400 educational pieces in a variety of formats with more than 100 translated across 5 languages, including English. As the site has evolved and developed over time we have added a wide array of additional materials to the portfolio and expanded our resources to include multimedia elements such as photographs and illustrations, podcasts, and more. As part of the development process the AUA and the Foundation have taken the appropriate steps to secure the rights to legally use these images in order to offer the site as a resource to AUA members, their patients and their practices. It is important to note that these permissions are not automatically transferrable to others who wish to utilize the content available on UrologyHealth.org.

In order to maximize the benefit of UrologyHealth.org–and minimize the risk of infringing the rights of content creators–a good best practice we share with members is to provide a link to the condition page you would like to share with your patients. This not only helps you to avoid conflicts with the developers of specific pieces of content (eg illustrations), but also ensures that you are sharing the most current content as the site is updated regularly with the newest information available.

In the September issue of AUA*News* our Judicial & Ethics Committee Chair Dr. Christian Twiss and General Counsel Diane Bieri, Esq., shared additional tips to ensure your practice is not only providing the best information available but also following proper protocols in how you develop and share online content from others.

The AUA and the Urology Care Foundation's patient education team are here to assist you. If you have questions or would like more information about our patient education materials or UrologyHealth.org, please contact us at info@UrologyCareFoundation.org. ◆

SPOTLIGHT *on Global Urology*

# Brazilian Membership Exceeds 1,000

**Angela Smith, MD, MS**
**AUA Assistant Secretary of Latin America and the Caribbean**
Chapel Hill, North Carolina

The AUA and the Sociedade Brasileira de Urologia (SBU) have worked together for more than a decade to improve urological education and patient care around the world. I am pleased to share that AUA's membership from Brazil is now over 1,000 members strong, a huge accomplishment and testament to the friendship and collaborative partnership that has been developed between our organizations. This success came about through a multifaceted approach of educational outreach that allows Brazilian urologists and residents to experience the value of AUA membership.

Brazil was one of the AUA's original international partners as outlined in our International Education Plan that was launched in 2007. Since then the AUA has consistently brought our educational benefits and resources to our friends and colleagues in Brazil. In 2009 the AUA launched the AUA/SBU Academic Exchange program. This reciprocal program allows 2 North American urologists to observe at an academic center or centers in Brazil and attend a SBU urology meeting while also allowing 2 Brazilian urologists to do the same in the United States. The program not only allows the sharing of

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## Spotlight on Global Urology

▼ Continued from page 32

knowledge and experiences but is also designed to foster a closer alliance between the AUA and SBU and assist in identifying future leaders within both organizations.

In 2012 the AUA held the Highlights of the AUA program in Brazil, the first ever of its kind. This program allows local urologists to present AUA Annual Meeting content in Portuguese during one of the SBU Regional Meetings. The Highlights program occurs on an annual basis and rotates around the country to enable urologists in every part of Brazil to benefit from the AUA's education that they may not be able to receive otherwise.

Of course, our strong partnership could not have been formed without committing to participate in each other's national urological meetings. I had the honor of attending the SBU meeting in Curitiba, Brazil last year along with other AUA participants. We received the utmost in hospitality, and it was a pleasure to witness the high quality education of the SBU meeting that hosts around 4,000 attendees. I was particularly impressed by the women in urology group, aptly named the Orchids. The Orchids held their first official meeting in Curitiba with record attendance thanks to the full support of the SBU board and their president, Dr. Sebastião Westphal. I was very proud to participate in their meeting and discuss further how the AUA and SBU can support the global efforts of women in the field of urology.

The SBU also sends a large delegation of Brazilian urologists to the AUA Annual Meeting each year. For nearly 10 years the AUA has held the Brazilian Portuguese Urology Program (BPUP) at our meeting. The program includes AUA and SBU experts talking on a variety of urological topics and garners 400 to 500 attendees. Many Brazilian urologists serve as moderators or speakers on the AUA program as well, further highlighting the strong bond between our associations.

As the AUA Assistant Secretary of Latin America and the Caribbean it has been an honor to become a part of the special partnership between the SBU and AUA over the last 2 years. Despite Covid-19's global impact and travel restrictions the pandemic has not stopped but rather strengthened our commitment to education. The SBU and AUA partnership continues to expand virtually, and the AUA will participate in the SBU Paulista Congress later this year.

I would like to sincerely and humbly acknowledge all of the SBU and AUA leaders that have preceded me in establishing this success and reaching this incredible membership milestone, especially Dr. Fernando Kim, AUA's Host Country Liaison to Brazil, and Dr. Luiz Torres, SBU's Chair of International Relations, who have worked tirelessly on these collaborative efforts. Both are kind, generous and innovative leaders with whom I have had the pleasure to work, innovate and learn. I look forward to continuing to build upon the foundation that has been established between the SBU and AUA, and I am confident that our friendship will remain strong long into the future. ◆

FROM THE *History Committee*

# Taking a History: Warfare Phallotomy and Trophy Taking

**Hannah E. Moreland**
Columbia, South Carolina

Of the many great causes of death the most controversial are those inflicted by warfare. The practice of human trophy taking, one of the most contentious of all wartime historical activities, includes the radical disfigurement of the vanquished following a massacre. These trophies would bestow honor and prestige upon the victor, yet this revengeful act was the ultimate display of dominance and power over the desecrated. Even if no trophy was taken mutilation was commonly inflicted upon the victims' corpses.

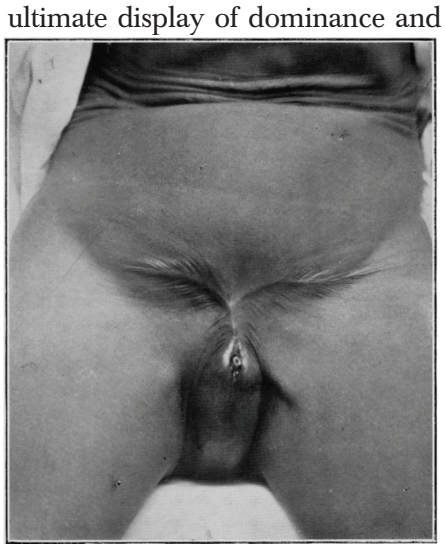

**Figure 1.** Mutilated victim in late 1800s Abyssinian conflicts.[6]

History is not lacking in examples, and this unique form of pillaging is more commonplace than one might think. The most blatant example of a trophy would be the human head itself, but urologically the genitals have historically been a prime target and continue to be of modern interest. Phallotomy is therefore defined as the removal of the penis possibly in combination with the scrotum and testicles (fig.1).

### Ancient Egypt

Since the first known hieroglyphics showing the taking of trophy penises this capacity for anatomical amputation has always been a nightmarish aspect of wars. During the ancient Egyptian empire 2 prominent pharaohs ordered their soldiers to collect the genitals of slain enemies. Thousands of penises (estimated at 13,240) were collected and presented to Ramses III following the battle of Khesef-Tamahu.[1] These offerings are depicted on the walls of Medinet Habu Temple where Ramses' subjects are seen laying enemy hands and penises at his feet (fig. 2).

**Figure 2.** Hieroglyphics on the Medinet Habu Temple showing offerings of enemy penises.[7]

"Libyans slain whose uncircumcised phalli were carried off" demonstrate the triumph of Merneptah's warriors over Libyan enemies.[1]

**Figure 3.** Narmer Palette (reprinted with permission).[8]

Merneptah memorialized his victory with inscriptions in the walls of the Temple of Karnak and on the Merneptah Stele. Similarly, the Narmer Palette shows a procession heading toward 2 rows of decapitated and bound enemies with their genitalia placed on their heads (figs. 3 and 4).[2] This detail depicts a victory celebration, and scholars have described the scene as "the execution and deliberate humiliation of enemy prisoners, decapitated and emasculated." The severed phalluses are displayed prominently as a way to "heap insult upon injury" to the slain enemies.[2]

### Violence in the Old Testament

There is no better (or worse, depending upon your point of view) example of the brutality of warfare than in the Old Testament.

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## From the History Committee

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In 1 Samuel 18:27 Saul offers his daughter to David for marriage in exchange for 100 Philistinian foreskins, whereby David delivers twice what is required: "David arose and went, he and his men, and slew of the Philistines two hundred men; and David brought their foreskins, and they gave them in full tale to the king."

**Figure 4.** Close-up of Narmer Palette.[8]

### Native Americans and the Sand Creek Massacre

In the Sand Creek Massacre of 1864 Colonel John Chivington led the Union army in an unprovoked attack on the Cheyenne and Arapaho villagers during which "fingers and ears were cut off the bodies for the jewelry they carried."[3] The body of Cheyenne Chief White Antelope was targeted, and in addition to scalping him the soldiers "cut off his nose, ears, and testicles – the last for a tobacco pouch."

### Modern Warfare

Although not as common an occurrence there are several notable examples of trophy taking in the modern era. During the Vietnam War the practice of fashioning enemy ears into a necklace and wearing it became popular. One soldier recalls "[wearing] them around our necks to show we were warriors, and we knew how to get revenge."[4] A 1944 issue of Life magazine published a photo showing a young American woman admiring a Japanese skull that her deployed boyfriend had sent her (fig. 5).[5] World War II memoirist E.B. Sledge described seeing a bloated, blackened corpse of a fellow Marine on the Pacific Island of Peleliu. His hands and feet were cut off, his severed penis stuffed in his mouth.[4]

Trophy taking is rooted in personal efficacy, power and status and is linked to intimidating adversaries. The barbarity of war itself seemingly can be capped only by the atrocities inflicted by the victor over the vanquished with the collection of anatomical relics. These dark trophies included the penis as an ultimate attempt to humiliate the conquered and is a stark reminder of transgressive objects used as punitive objects of remembrance, a

**Figure 5.** 1944 *Life* magazine "Picture of the Week."[5]

macabre memento mori.

Defilement by phallotomy does deserve an altogether different connotation and categorization from the memento mori that trivializes the victim's death to one of casual brutality. Phallotomy implies an intent far more than simple trophy taking. Explanations include ritualized defilement, an attempt to take a further step toward defiling the dead. However, the ancients probably collected penises because they were small, solitary and a method of keeping score for remuneration by their leaders. The penis as a trophy of war was thus a convenient symbol, even more so than the head, the ears, hands or whatever else the warrior might select. The penis had long ago acquired the stigmata of virility, and it should come as no surprise that in the long and violent history of warfare it should have achieved some renown as a talisman of death.

*Winner of the 2020 AUA Earl Nation Retrospectroscope Award.* ◆


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## FROM THE *Public Policy Council*

# Advocacy in Urology: Our Year in Review

**Eugene Y. Rhee, MD, MBA**
**Chair, AUA Public Policy Council**
San Diego, California

Swimming early this morning while the sun began to rise, I reflected on the global events unfolding before us and how we seek to adapt and continue our work as urologists in our communities. The continued success of AUA's health policy work has been our ability to quickly adapt our advocacy toward the real-time global issues impacting the urological community. We have met with federal agencies to discuss proposed policies for expanding the use of telehealth and the valuation of specific urology services. We had hundreds of virtual meetings with members of Congress that ultimately contributed to the House's September 22 passage of the Veteran's Prostate Cancer Treatment and Research Act (H.R. 6092) as well as the introduction of H.R. 5924, which would create a student loan forgiveness program for specialty physicians who practice in a rural areas.

Our multipronged advocacy strategy to retain postpandemic telehealth waivers was developed as AUA's Urology Telehealth Task Force saw 2019 usage levels increase from approximately 10% in 2019 to metrics as high as 80% use in some institutions as a response to COVID-19.

Telehealth was one of 2 advocacy "asks" during the 2020 Virtual Annual Urology Advocacy Summit that took place from August 31 to September 3. AUA members representing 34 states held 160 virtual Hill visits with lawmakers and staff from the offices of 67 senators and 102 representatives to discuss telemedicine and the urology workforce. The event also featured a panel session on telehealth and COVID-19 for more than 300 AUA Summit attendees, 81 of whom were medical students, residents, fellows or young urologists.

This special session on telemedicine complemented a meeting with the Centers for Medicare & Medicaid Services and formal comments in support of policies that provide physicians with the flexibility to ensure that they are able to provide services to beneficiaries using audio and video communications technology.

The AUA also seeks the patient voice in our advocacy strategy. This year the AUA's Patient Advocacy Connections Program successfully connected more than 50 participants from 35 urology focused patient advocacy organizations during a 3-day Lunch & Learn series. The program included 2 engaging roundtable discussions where conversations addressed key challenges, including prevention, access and partnerships, and also focused on effective advocacy communication strategies that included panelists representing the patient, physician and research perspective.

Lastly, even as efforts were focused on humanitarian giving for much of the year the AUA was also able to continue its participation in political advocacy. AUAPAC supported nearly a dozen

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## HAVE YOU *Read?*

**Daniel A. Shoskes, MD**
Columbus, Ohio

**Watanabe J, Akiyama Y, Niimi A et al: Clinical characterization of interstitial cystitis/bladder pain syndrome in women based on the presence or absence of Hunner lesions and glomerulations. Low Urin Tract Symptoms 2020; doi:10.1111/luts.12344.**

The AUA guidelines on interstitial cystitis say that Hunner's lesions (HL) are a clinically relevant finding and glomerulations are not, yet I see patient after patient who comes for a second opinion with images of glorious glomerulations in hand. What does the contemporary evidence show? In this study the clinical records of 100 female patients with interstitial cystitis/bladder pain syndrome (IC/BPS) who underwent their first bladder hydrodistension were retrospectively reviewed. They were divided into patients having (HL-IC, 57) or lacking (BPS, 43) HL. Patients with BPS were further classified as those with (29) and without (14) glomerulations. Among these 3 subtypes, demographics, comorbidities, symptom parameters including a visual analog scale for pain scores, O'Leary and Sant Symptom and Problem (OSSI/OSPI) Indices, frequency volume chart variables, and bladder capacity at hydrodistension were compared.

Patients with HL-IC were older and had higher OSSI/OSPI scores, greater daytime frequency and nocturia, reduced maximum and average voided volumes, and smaller bladder capacity at hydrodistension compared with patients with BPS. Pain intensity and illness duration were comparable among the 3 groups. Patients with HL-IC had autoimmune disorders as comorbidities more often but had psychiatric disorders and irritable bowel syndrome less often compared with patients with BPS. No discernible differences in clinical characteristics of symptom severity and comorbid disorders were evident between BPS with and without glomerulations.

The authors conclude that the presence of HL is associated with distinctive clinical characteristics while glomerulations are not in female patients with IC/BPS. The presence of HL but not glomerulations is a robust phenotypic feature of IC/BPS in women.

To this I add: If you see HL, do not forget fulguration, intralesional steroids or cyclosporine.

**Streur CS, Moloci NM, Kraft KH et al: Trends in procedures to initiate renal replacement therapy among people living with spina bifida. J Urol 2020; doi:101097/JU0000000000001314.**

Long-term survival of young patients with congenital or acquired neurogenic bladders is one of the true urological success stories of the last 100 years. Are we still preserving the kidneys attached to these bladders? In this study the authors examined population based data to measure the frequency of procedures to establish renal replacement therapy, a marker for end stage kidney disease, among patients with spina bifida. They used the State Inpatient Database and State Ambulatory Surgery and Services Databases from Florida, Kentucky, Maryland and New York (2000 to 2014), which include encounter level data. With a diagnosis code based algorithm they identified all procedural encounters made by patients with spina bifida. They determined the percentage of these encounters that were for facilitating renal replacement therapy (ie arteriovenous anastomosis, renal transplantation).

Of all procedures performed on patients with spina bifida during this time the proportion of procedures performed to establish renal replacement therapy significantly decreased in the inpatient ($p=0.042$) and outpatient setting ($p<0.001$). People with spina bifida undergoing procedures to establish renal replacement therapy were on average young adults (mean age 34.5 and 36.0 years, respectively) with a high prevalence of hypertension (75.8% and 68.6%, respectively).

The authors conclude that the frequency of surgeries to initiate renal replacement therapy among people with spina bifida undergoing procedures is low and is not increasing. This highlights the importance of consistent care throughout adolescence and young adulthood and hypertension screening.

**Lundy SD, Parekh NV and Shoskes DA: Obstructive sleep apnea is associated with polycythemia in hypogonadal men on testosterone replacement therapy. J Sex Med 2020; 17: 1297-1303.**

I have been writing this monthly feature now for almost 3 years and assiduously avoided quoting my own papers. I think this one has a valuable clinical take home point, so I will cross into editorial nepotism just this once.

Polycythemia is a known side effect of testosterone replacement therapy (TRT) and appears to correlate with maximum testosterone (T) levels. There is also a well-established association between obstructive sleep apnea (OSA) and the development of polycythemia, which confers additional long-term cardiovascular morbidity. Synergy between TRT and OSA in the development of polycythemia remains poorly understood. The objective of this study was to retrospectively assess the relationship of OSA and secondary polycythemia in hypogonadal men receiving TRT.

We performed a retrospective chart review of men treated from 2015 to 2019 for the diagnosis of hypogonadism. Patients who developed a hematocrit of 52% or greater were classified as having polycythemia. OSA was identified via clinical documentation or use of nocturnal continuous positive airway pressure. Demographics, laboratory values, treatment details and comorbidities were recorded.

We included 474 men in this study, of whom 62 (13.1%) met the criteria for the diagnosis of polycythemia with a median hematocrit of 53.6% (IR 52.6–55.5). Univariate analysis demonstrated a strong positive association between polycythemia and the concomitant diagnosis of OSA in hypogonadal men ($p=0.002$). Even after correcting for age, body mass index (BMI) and peak T levels in the multivariate analysis ($p=0.01$) this relationship remained significant with an OR of 2.09 (95% CI 1.17–3.76). We included 37 men on TRT with polycythemia and OSA in the final cohort with a mean age of 59.2±11.4 years, mean BMI of 32.4±6.0 and median time from TRT initiation to polycythemia diagnosis of 3 years. All patients diagnosed with OSA were prescribed continuous positive airway pressure with poor compliance noted in 52.8% of men. In all, 37.8% were managed via phlebotomy and 59.5% were managed via dose de-escalation of TRT. In hypogonadal men on TRT with polycythemia BMI was the only risk factor strongly associated with OSA ($p=0.013$).

We concluded that the development of polycythemia in hypogonadal men on TRT was associated with an increased prevalence of OSA. In hypogonadal men (particularly those with elevated BMI) on TRT who develop secondary polycythemia a diagnosis of OSA should be strongly considered. ◆

## From the Public Policy Council

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candidates in 2020 largely focusing on Republicans and Democrats in both chambers who care about policies that are critical to urological specialists and the patients they serve. Timely issues such as expanding telehealth services, addressing health care disparities and expanding federal research funding were all priorities for AUAPAC in 2020.

Through the chaos of politics, social change can become transformative but requires persistent advocacy. The global pandemic has reaffirmed that good policy ideas rely on sound legislative action, political action committee work and persistent engagement with patient advocates. For more information about AUA's policy work please visit us at http://www.auanet.org/advocacy/advocacy-overview. ◆


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