Update on Clinical Trials of Restorative Therapies for Erectile Dysfunction

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Erectile dysfunction (ED) refers to the inability to achieve or maintain an erection sufficient for satisfactory sexual performance and has significant negative impact on men and their partners. Initial treatments include couples therapy, oral pharmacological agents (namely PDE5 inhibitors) as well as local pharmacotherapies to the penis including intra-urethral and self-intracavernous injections. Although these treatments demonstrate good efficacy for men with mild to moderate ED, there remains a cohort who either cannot tolerate these medications, have direct contraindications or represent a hard to treat ED population. These include men with postprostatectomy ED, diabetes mellitus, severe ED as it relates to peripheral vascular disease and smoking. In the field of sexual medicine we recognize the importance of spontaneous physiological erections, which most men and their partners report as a preference to pharmacological and surgical approaches to ED. Therefore, the field has sought approaches that reverse organ dysfunction and restore normal neurovascular function of the penile vasculature.

Restorative therapies, based on the concept of repairing or replacement of diseased tissue by stimulating endogenous regenerative capabilities, provide a promising alternative to the current treatment paradigms, transitioning from modalities that only address disease symptoms to interventions aimed at restoring structure and function of erectile tissue. Restorative therapies include regenerative medicine therapies such as stem cell therapy (SCT) or platelet rich plasma (PRP) and technologies based on regenerative principles such as low intensity shock wave therapy (LiSWT), which stimulates endogenous stem cell mobilization to diseased tissue. Many of these erectorgonic treatments have already been studied preclinically and are in early phase clinical trials. However, randomized control trials that are appropriately powered with placebo arms do not exist, thereby limiting the widespread acceptance of restorative therapies for ED into standard clinical practice. I will summarize the current state of understanding of LiSWT and PRP for management of ED. Additional commentary for SCT can be found in the Sexual Medicine Society of North American (SMSNA) position statement.1

The cumulative results from numerous clinical trials looking at LiSWT are promising. Likewise, across all trials there were no documented adverse events with various LiSWT treatment protocols. Therefore, at a bare minimum LiSWT within the parameters of studies performed is safe. However, the shockwave generator types and protocols (energy settings, dosing, frequency of use, probe locations and duration of therapy) will summarize the current state of LiSWT and PRP for management of ED. Additional commentary for SCT can be found in the Sexual Medicine Society of North American (SMSNA) position statement.1

SipIT Intervention to Increase Fluid Intake for Stone Prevention

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Increasing fluid intake is a well-established strategy for kidney stone prevention. However, adherence to guideline recommendations to increase fluid consumption to produce more than 2.5 L urine output per day is commonly below 50%.1 Reliance on patient education to drink more, thirst and memory are not enough to meet fluid intake goals. Poor adherence, high recurrence and costs associated with kidney stones highlight the need for new tools to address disease-specific barriers. Wearable technology is becoming more prevalent and may be used to support a variety of health behaviors. It offers a new opportunity to support adherence to preventative strategies such as increasing fluid intake that require lifestyle behavior modification. With limitations of currently available technology there is a need for new technology that can identify lapses in drinking behavior in real
In non-muscle invasive bladder cancer (NMIBC) is there space to do more after BCG?

When BCG fails, radical cystectomy is the only AUA-recommended treatment option for patients with high-risk NMIBC. Additional therapies after BCG failure could help patients, especially those who are ineligible or unwilling to undergo surgery.¹

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Clinical Trials of Restorative Therapies for ED

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were inconsistent among studies and consequently difficult to compare. Therefore, a clinical study exploring the types of shockwave (electrohydraulic, electromagnetic and piezoelectric) would be beneficial. Similarly, given the broad spectrum of treatment protocols future clinical trials should attempt to provide some standardization in device settings as well as duration of treatment. This would allow for larger multicenter studies and enable comparison among trials. In particular, an area of interest is the durability of treatment response since some hypothesize that maintenance dosing after initial treatment may be more beneficial for efficacy.

The regenerative potential of platelet rich plasma, autologous blood plasma with supraphysiological concentrations of activated platelets, was first described in the 1980s. Despite the widespread adoption of PRP, biological underpinnings remain poorly understood. Limited preclinical data demonstrate that PRP is comprised of a rich milieu of growth factors (platelet derived growth factor, insulin like growth factor, vascular endothelial growth factor, epidermal growth factor, fibroblast growth factor) and activated platelets that work synergistically to facilitate mitogenesis and neo-angiogenesis, thereby reconstituting diseased tissues. PRP can be prepared by sequential centrifugation of whole blood with removal of red blood cells and platelet poor plasma followed by the addition of a platelet activating factors. PRP can provide the mechanisms of action and pathways are critically important, and randomized controlled trials of larger cohorts are needed before any claims about efficacy or safety can be made.

The potential for restorative therapies is high. However, there is a paucity of well-conducted clinical trials proving the efficacy and durability of these interventions. At present, the current position of the SMSNA regarding restorative therapy for management of ED should be limited to rigorous and well-designed clinical trials.1 The cumulative body of clinical trials for restorative therapies is largely incomplete, and many questions remain unanswered. The clinical studies have shown safety and feasibility, but efficacy has not been established. Future studies using standardized protocols, adequate controls and substantial long-term followup are necessary. At the current time there may not be enough clinical data in appropriately powered clinical trials. However, the future is bright as there are ongoing well-designed trials that will provide the clinical evidence and protocols necessary for restorative therapies to be used widely in clinical practice. Until then, restorative therapies should not be offered in routine clinical practice. ♦

SipIT Intervention for Stone Prevention

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time to yield sustainable behavior modification.

To address this need, in collaboration with colleagues in kinesiology and preventative medicine, Dr. David Conroy at Pennsylvania State University, and computer science, Dr. Edison Thomaz at University of Texas-Austin, we developed a novel technology, sipIT intervention. For the first time we propose to overcome the limitations of existing approaches by classifying drinking behavior from wrist worn inertial sensors to trigger context sensitive, just-in-time reminders that promote fluid consumption. This approach eliminates the need to self-monitor and minimizes burden by delivering reminders to drink only when patients have not had a drink recently.

Recognizing the importance that any new intervention must not only be efficacious but must also be acceptable to patients for health behavior changes to be maintained, the development of sipIT intervention has been guided by a co-design approach using patient input. Patients have interest in the use of consumer wearable devices to support fluid intake (Fitbit, connected water bottles), and the use of connected water bottles has been shown to provide accurate measurement and increase fluid intake.2–4 We previously demonstrated that wrist worn sensors with accelerometers can detect drinking behavior to provide automated lapse detection in fluid intake in the lab setting.5

From these studies we developed the sipIT intervention, which is a context sensitive behavior change system that incorporates a wrist worn sensor (Fitbit Versa watch), a custom sipIT watch app with an algorithm for drinking gesture detection, connected water bottle (H2oPal), self-monitoring through a smartphone app and a backend server that mediates data transfer between devices (figs. 1 and 2).

The H2oPal connected water bottle has an accelerometer and weight sensor. It takes a measurement each time the user takes a drink (or refills) and sets the bottle back down. This unique technology allows for all fluid types to be used in the bottle, and the sensor can fit onto most water bottles with a 3-inch base, which addresses the limitations of other consumer connected water bottles.

The sipIT intervention combines

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SipIT Intervention for Stone Prevention

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the 3 evidence-based behavior change techniques of planning to drink at regular intervals, prompts to remind patients to drink if they have not reached the goal and negative reinforcement to shape desirable behavior by withholding disruptive notifications when patients have met the goal. These techniques were selected to facilitate fluid consumption habit formation.

We performed a 3-month trial to determine the feasibility and acceptability of sipIT intervention in the clinical setting. In addition, we evaluated the changes in perceived barriers to increasing fluid intake. Patients with a history of kidney stones (31, 58% female, age 40.02-14.3 years) were recruited from the community and a kidney stone specialty clinic to participate. Patients with iPhones® were given a Fitbit Versa watch with the sipIT gesture detection app installed and an H2oPal (Out of Galaxy Inc., Wilmington, Delaware) connected water bottle. Training was provided to learn how to use the digital health tools, and patients received education about fluid intake guidelines for kidney stone prevention. Participants completed questionnaires to determine perceived barriers to increasing fluid intake at baseline, 1 and 3 months. Retention rates were high at 1-month (90%) and 3-month (87%) assessments. After the first month of intervention, patients reported that forgetting to drink and lack of thirst were less of a barrier to meeting fluid intake goals, which continued at 3 months (fig. 3). The majority of participants perceived that the sipIT intervention helped them to achieve their fluid intake goals (83%).

The sipIT intervention may be used to detect drinking behavior and provide automated lapse detection in fluid intake in the clinical setting with just-in-time messaging reminders. The system was acceptable to patients, and there was a reduction in common perceived barriers to fluid intake. Combining digital tools with behavioral science may help to improve adherence to fluid intake recommendations. Future studies will examine the efficacy of the sipIT system to increase daily fluid consumption and 24-hour urinary output. If successful in developing technology to improve fluid consumption with long-term efficacy this could have a significant impact on the reduction of kidney stones, which could improve the quality of life for stone formers and substantially reduce the economic burden of kidney stones.

AUA 2020 Virtual Science Best Poster winner.

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Figure 3. SipIT intervention reduced common perceived barriers to fluid intake.

A Urine Based Test to Monitor Neoadjuvant Therapy in Bladder Cancer

With more than 80,000 new cases and almost 18,000 deaths per year in the United States, bladder cancer is one of the most common and lethal malignancies treated by urologists. Neoadjuvant chemotherapy followed by radical cystectomy has been a standard of care in patients with muscle invasive disease for more than a decade. The landmark SWOG 8710 trial showed that chemotherapy plus surgery provides an overall survival benefit compared with cystectomy alone. However, this benefit is greatest in patients who have a complete response to neoadjuvant therapy and is limited in those with only partial response. Unfortunately, up to 70% of patients will have residual disease at the time of cystectomy. The modern era of personalized medicine has been marked by efforts to produce novel therapies and to predict who may benefit from such therapies. Predictive algorithms include clinical models to risk stratify patients before neoadjuvant therapy, surgical restaging with transurethral resection after neoadjuvant therapy and molecular markers to predict pathological response at the time of surgery. Despite these efforts, accurate prediction of response remains elusive.

Earlier work from the University of Southern California has shown the ability of noninvasive urine based epigenetic testing for DNA methylation to monitor treatment in nonmuscle invasive bladder cancer. Given the need for better tools in muscle invasive disease, ongoing work now assesses the ability of a novel urine based epigenetic assay to monitor response to neoadjuvant therapy.

Currently, urine samples are collected from all patients with muscle invasive bladder cancer who undergo neoadjuvant therapy with chemotherapy or immunotherapy under an institutional review board approved protocol. Urine is collected at baseline before any systemic therapy and with each subsequent cycle of therapy. Samples are then analyzed with the Bladder CARE test, an assay developed by Pangea Laboratories (Irvine, California). This is a urine based assay that measures the DNA methylation levels of 3 bladder cancer-specific biomarkers (TRNA-Cys, SIM2 and NXX1-1) and 2 internal control loci using methylation sensitive restriction enzymes coupled with qPCR.

Results are reported with the Bladder CARE Index (BCI) score and categorized as “positive,” “high risk,” or “negative.” These scores are proportional to the concentration of cancer cells in the sample. Changes in the BCI score and surgical pathology are then reviewed to determine association.

Preliminary results from this study were recently reported. This preliminary analysis included 10 patients who completed neoadjuvant therapy and underwent cystectomy. The majority (70%) received gemcitabine and cisplatin (GemCis, see Appendix). Histology included urothelial carcinoma without or with differentiation in all patients but 1, who had a neuroendocrine tumor. BCI score decreased in 7/10 (70%) patients (see figure). Of these 7 patients 6 (86%) showed at least a partial response to neoadjuvant therapy including 5/6 (83%) patients with pure urothelial histology and 5/6 (83%) patients who received GemCis. One patient with complete response on final pathology had a negative BCI score at baseline and throughout therapy (#7). Of the 4 patients with weak or no change in BCI score (#3, 11, 12, 14), all had residual disease at the time of cystectomy, 2 (50%) had variant histology (#3, 12) and 2 (50%) received neoadjuvant therapies besides GemCis (#12, 14).

These results show that the Bladder CARE test may be useful in monitoring and predicting response to neoadjuvant therapy in patients with muscle invasive bladder cancer. It remains to be elucidated whether the utility of the Bladder CARE test depends on tumor histology or type of therapy administered. Further studies are underway to evaluate the utility of this test.

**Appendix.** Clinicopathological characteristics and BCI scores of 10 patients undergoing neoadjuvant therapy for muscle invasive bladder cancer.

<table>
<thead>
<tr>
<th>ID</th>
<th>cTN</th>
<th>Histology</th>
<th>NAT</th>
<th>pT</th>
<th>Initial BCI</th>
<th>Final BCI</th>
<th>%Δ BCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>T4N0</td>
<td>UC</td>
<td>GemCis</td>
<td>TisN1</td>
<td>High risk</td>
<td>Negative</td>
<td>84.8</td>
</tr>
<tr>
<td>3</td>
<td>T2N0</td>
<td>UC glandular</td>
<td>GemCis</td>
<td>TisN0</td>
<td>Positive</td>
<td>High risk</td>
<td>-54</td>
</tr>
<tr>
<td>5</td>
<td>T3N0</td>
<td>UC</td>
<td>GemCis</td>
<td>TON0</td>
<td>Positive</td>
<td>High risk</td>
<td>-95</td>
</tr>
<tr>
<td>7</td>
<td>T2N0</td>
<td>UC</td>
<td>GemCis</td>
<td>TON0</td>
<td>Negative</td>
<td>Negative</td>
<td>-45.5</td>
</tr>
<tr>
<td>8</td>
<td>T4aN0</td>
<td>UC</td>
<td>GemCis</td>
<td>TON0</td>
<td>Positive</td>
<td>Negative</td>
<td>-99.8</td>
</tr>
<tr>
<td>9</td>
<td>T3N0</td>
<td>UC</td>
<td>GemCis</td>
<td>T2bN0</td>
<td>High risk</td>
<td>Negative</td>
<td>-82.3</td>
</tr>
<tr>
<td>11</td>
<td>T2N0</td>
<td>UC</td>
<td>GemCis</td>
<td>T2bN0</td>
<td>Positive</td>
<td>Positive</td>
<td>-59.9</td>
</tr>
<tr>
<td>12</td>
<td>T3N0</td>
<td>Small cell</td>
<td>Carbo</td>
<td>Etop</td>
<td>T2bN0</td>
<td>Positive</td>
<td>148</td>
</tr>
<tr>
<td>14</td>
<td>T2N0</td>
<td>UC</td>
<td>Pembrolizumab</td>
<td>Epithelial</td>
<td>T2bN0</td>
<td>Positive</td>
<td>64.4</td>
</tr>
<tr>
<td>15</td>
<td>T3N0</td>
<td>UC</td>
<td>Pembrolizumab</td>
<td>Epithelial</td>
<td>T2bN0</td>
<td>Positive</td>
<td>94.7</td>
</tr>
</tbody>
</table>

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) 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.

Fractures — In a randomized study (SPARTAN), fractures occurred in 12% of patients treated with ERLEADA® and in 7% of patients treated with placebo. In a randomized study (TITAN), 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% (0.9%); 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% (0.9%); hyperglycemia ERLEADA® 70% (2%), placebo 59% (1%); hypertriglyceridemia ERLEADA® 67% (2%), placebo 49% (0.6%); hyperkalemia ERLEADA® 32% (2%), placebo 22% (0.3%).
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 CYP2C3 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 (2.7)].

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

ADT = androgen deprivation therapy, HR = hazard ratio, mCSPC = metastatic castration-sensitive prostate cancer, nmCRPC = metastasis-free survival, mPSA = metastasis-sensitive prostate cancer, mPFS = metastasis-free survival, nmPSA = non-metastasis-sensitive prostate cancer, PSA = prostate-specific antigen, RFS = radiographic progression-free survival, SPARTAN = Selective Prostate Androgen Receptor Targeting with ARN-214, TITAN = Targeted Investigational Treatment Analysis of Novel Androgen Receptor.

**References:**

1. ERLEADA® [Prescribing Information.] 

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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, sepsis, 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 6% of patients, most commonly from rash (2%). Adverse reactions leading to dose interruption or reduction of 1, or discontinuation of ERLEADA occurred in 23% of patients; the most frequent (≥1%) were rash, fatigue, and hypotension. Serious adverse reactions occurred in 26% of ERLEADA-treated patients and in 22% of 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. Among these reactions, the most frequent (≥5%) in the ERLEADA arm compared to placebo.

Table 1: Adverse Reactions in TITAN (mCSPC)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ERLEADA N=524</th>
<th>Placebo N=527</th>
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</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Fad</td>
<td>31</td>
<td>23</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissues disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Other</td>
<td>88</td>
<td>84</td>
</tr>
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</table>

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Table 2: Laboratory Abnormalities Occurring in ≥5% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference > 5% in Graded (≥3) Incidence in mCSPC)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA N=803</th>
<th>Placebo N=528</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Hematopoiesis</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>42</td>
<td>30</td>
</tr>
<tr>
<td>Anemia1</td>
<td>70</td>
<td>59</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>70</td>
<td>59</td>
</tr>
<tr>
<td>Neutropenia2</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Does not reflect fasting values</td>
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</table>

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

<table>
<thead>
<tr>
<th>System/Orган Classification and Administration site conditions</th>
<th>ERLEADA N=583</th>
<th>Placebo N=528</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Metabolic and nutritional disorders</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Liver injury</td>
<td>10</td>
<td>7</td>
</tr>
</tbody>
</table>

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Table 4: Laboratory Abnormalities Occurring in ≥5% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference > 5% in Graded (≥3) Incidence in nmCRPC)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA N=583</th>
<th>Placebo N=528</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>70</td>
<td>59</td>
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</table>

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Table 5: Adverse Reactions in TITAN (mCSPC) (continued)

<table>
<thead>
<tr>
<th>System/Organ Classification and Administration site conditions</th>
<th>ERLEADA N=524</th>
<th>Placebo N=527</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Hematologic disorders</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>11</td>
<td>7</td>
</tr>
</tbody>
</table>

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Table 6: Laboratory Abnormalities Occurring in ≥5% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference > 5% in Graded (≥3) Incidence in nmCRPC)

<table>
<thead>
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<th>Laboratory Abnormality</th>
<th>ERLEADA N=583</th>
<th>Placebo N=528</th>
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<tr>
<td>All Grades</td>
<td>%</td>
<td>%</td>
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<tr>
<td>Hematologic disorders</td>
<td>70</td>
<td>59</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>11</td>
<td>7</td>
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</table>

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Table 7: Adverse Reactions in TITAN (mCSPC) (continued)

<table>
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<tr>
<th>System/Organ Classification and Administration site conditions</th>
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<th>Placebo N=527</th>
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</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Metabolic and nutritional disorders</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>11</td>
<td>7</td>
</tr>
</tbody>
</table>

ERLEADA® (apalutamide) tablets

Table 8: Laboratory Abnormalities Occurring in ≥5% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference > 5% in Graded (≥3) Incidence in nmCRPC)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA N=583</th>
<th>Placebo N=528</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>70</td>
<td>59</td>
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</tbody>
</table>

ERLEADA® (apalutamide) tablets

Table 9: Adverse Reactions in TITAN (mCSPC) (continued)

<table>
<thead>
<tr>
<th>System/Organ Classification and Administration site conditions</th>
<th>ERLEADA N=524</th>
<th>Placebo N=527</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Metabolic and nutritional disorders</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>11</td>
<td>7</td>
</tr>
</tbody>
</table>

ERLEADA® (apalutamide) tablets

Table 10: Laboratory Abnormalities Occurring in ≥5% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference > 5% in Graded (≥3) Incidence in nmCRPC)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA N=583</th>
<th>Placebo N=528</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Hematologic disorders</td>
<td>70</td>
<td>59</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>11</td>
<td>7</td>
</tr>
</tbody>
</table>
DRUG INTERACTIONS

Effect of Other Drugs on ERLEADA

Strong CYP3A4 or CYP3A4 Inhibitors

Co-administration of a strong CYP3A4 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 CYP3A4 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 UGT1A1, UDP-glucuronosyltransferases (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 DATP1B1 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 (DATP1B1) clinically. At steady-state, apalutamide reduced the plasma exposure to fexofenadine (a P-gp substrate) and rosuvastatin (a BCRP/DATP1B1 substrate). Concomitant use of ERLEADA with medications that are substrates of P-gp, BCRP, or DATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP or DATP1B1 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].

USING 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 toxicity studies were not conducted with apalutamide.

Lactation

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 (12.1) 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 40% 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 has been 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.

Inform patients that 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 (2.2) in full Prescribing Information].

Inform 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].

Manufactured by

Janssen Ortho LLC
Gurabo, PR 00778

Manufactured for

Janssen Products, LP
Gurabo, PR 00778

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Egydio Paradigm: An Innovative Strategy for Nongrafting Penile Enlargement

Introduction
The Tunica Expansion Procedures (TEP) Strategy is the newest improvement of lengthening techniques without grafting accompanied by prosthesis implantation.1-5 TEP evolved from grafting to nongrafting after a period of 2 decades of continuous development while searching for individualized solutions and enhancements for patients with penile size inadequacy (PSI). For an up-to-date review of the progressive treatment for PSI, see Wilson et al.6

Objective
• PSI can be acquired due to numerous retractive conditions including Peyronie’s disease, diabetes, pelvic surgery, radiotherapy, aging, and any other fibrotic condition.
• Preoperative diagnosis of PSI offers the option of intraoperative enlargement together with penile prosthesis.
• Prosthetic implantation is not associated with enlargement but only with axial rigidity.
• Enlargement is limited to the length of the urethra and the dissected neurovascular bundle (NVB) to be determined only intraoperatively.
• Multiple small incisions are arranged on the tunica in alternate, staggered rows, horizontal for lengthening and vertical for widening.
• The TEP Strategy uses a mathematical principle for optimal ratio of tunica expansion versus strength to permit the largest corporal volume possible for containment of cylinders of maximum capacity in length and girth.1-5

Methods
• From February 2016 through February 2019, 416 patients with PSI underwent the TEP Strategy with an average penile gain of 3.3 cm (range 2-6) measured intraoperatively.1-5
• Implantation of penile prosthesis was indicated since all had therapy resistant erectile dysfunction (ED) and were unable to engage in sexual intercourse.
• Preoperative stretch length tests and pharmacologically induced erections were used to compare current length and girth with patients’ subjective recollection of former penile dimensions.
• To prevent unrealistic expectations patients were fully informed that maximum enlargement for PSI is limited by anatomical features including the length of the urethra and dissected NVB and that the extent of penile enlargement can only be determined intraoperatively.
• The International Index of Erectile Function (IIEF) was completed before the surgery, and IIEF and Erectile Dysfunction Inventory of Treatment Satisfaction (EDITs) were administered after 6 months.

The TEP Strategy: A Blend of Science, Art and Intuition

The science of tissue expansion was reported as a mathematical formula by Vandeput et al.7 Patterns of cuts made by 18 dermatomes increased or decreased the ratio of tissue expansion according to variable lengths of cuts (L) and distances between cuts (b) and (d) (fig. 1).

Art blends the 3 variables of (L), (b) and distance between rows (d) to individual penile anatomies to obtain ideal relationships of tunica tissue expansion and strength. Vertical incisions provide tunica girth expansion and correction of indentations and hourglass deformity. Horizontal incisions provide lengthening on the penile shaft other than in areas of vertical incisions. If there is no constriction, vertical incisions may not be necessary unless the patient requires or desires additional girth.

Intuition is the ability to make spontaneous, intraoperative decisions about (L), (b) and (d) based on penile curvature, shaft constriction, loss of size and girth, calcification, and the limits of the urethra and the dissected NVB.

The TEP Strategy promotes tissue expansion while maintaining tunica strength to increase the penile volume and allow cylinders of maximum capacity inside the corpora without grafting. Since penile prostheses only provide axial rigidity, correction of PSI and enlargement of the visible penis during implant surgery may also be required or desired. Evolving techniques of tunica expansion have now made it possible to avoid grafting and preservation of the cylindrical appearance without dents and bulging.

Figure 1. Multiple small cuts are arranged in alternate staggered rows. Expansion increases directly proportional to length of cuts (L) and decreases inversely with intact distances between cuts (b) and distances between rows (d).

Figure 2. A, NVB is dissected starting with longitudinal, paraurethral incision on Buck’s fascia. B, eversion of glans permits dissection of NVB to expose tunica for tissue expansion and subsequent distal anchorage of cylinders.

Figure 3. A, stretch penis test showing dissected NVB without urethral mobilization and potential lengthening to its limits. B, schematic representation showing maximum length restoration to limits of urethra and NVB after application of TEP Strategy. C, surgical image of stretch penis test showing maximum lengthening obtained to limits of NVB without need for urethra dissection or elevation. (Selection of cylinder size, whether malleable or inflatable, can only be made after completion of enlargement. This case permitted lengthening of 3.5 cm.)

▼ Continued on page 11
Surgical Procedure

- Subcoronal incision and degloving provide adequate exposure of the shaft to enable application of the TEP Strategy.1,5
- The reservoir of a 3-piece prosthesis is inserted with the bladder empty to eliminate the need for a urethral catheter.
- An incision is made into the Buck’s fascia followed by dissection of the NVB (fig. 2).
- Expansion occurs perpendicular to the incisions with suggested lengths typically 5 to 8 mm (0.197–0.315 inches) and intact bridges of tissue and distances between parallel rows of 2 to 3 mm (0.079–0.118 inches) to promote expansion and preserve strength.
- If necessary, incisions (L) may be extended or added for better expansion or reduced with sutures to create new bridges (b) for prevention of dents or bulging.
- The urethra is more elastic and need not be dissected, detached, or elevated during the application of the TEP Strategy.1,5
- Incisions are made to the maximum depth of the entire tunica or scar tissue, but there is no need to pierce the cavernous tissue.
- Choice of cylinder size is determined only after completion of tissue expansion to minimize the use of rear tip extenders (fig. 3).
- After obtaining maximum tunica expansion, the cavernous body is measured for inflatable or malleable cylinders, rear tip extenders only if required, and optimum axial rigidity.
- Calcifications need not be removed, because incisions and expansions are applied in adjacent areas of the tunica around the circumference of the shaft.
- Vertical incisions provide tunica girth expansion while horizontal incisions provide lengthening (fig. 4).
- Vertical and horizontal incisions should not be crossed because they weaken the tunica and may result in bulging and insufficient strength to contain inflatable cylinders.

Conclusion

The Egydio TEP Strategy is the blending of science, art and intuitive applications of multiple small staggered rows of incisions on the tunica albuginea into a non-grafting technique, which increases penile length and girth while maximizing cylinder capacity.1,3 The technique has proven safe and effective to treat PSI when carefully administered to selected patients. The legacy is the continuing search and evolution of innovative techniques for penile enlargement associated with size reduction, curvature or shaft constriction. Future research for lengthening of the urethra and the NVB is needed to provide additional solutions to treat congenital or acquired penile size inadequacy.


INVEST IN YOURSELF. Invest in AUA Membership.

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Telehealth is a catchall term referring to the different ways information can be exchanged between providers and patients to educate, evaluate and make medical decisions. In 2016 the American Urological Association telehealth taskforce published a white paper highlighting the potential for telehealth to transform urological care, expediting care delivery, improving access to care and lessening the impact of the anticipated workforce shortage within urology. That same year Michigan Medicine’s Department of Urology established a telehealth program that provided established patients the option to followup with their urologist using video visits.

Video visits are real-time telehealth encounters in which patients connect with their providers through a video conferencing platform. Earlier work has highlighted patient benefits when following up through video visits including decreased travel time, lower costs, increased convenience and high patient satisfaction. However, there has been a lack of data evaluating the real-world impact of telehealth on measures of clinical efficiency and reimbursement. Our team identified 250 completed video visits and matched them to a random sample of 250 clinic return visits stratified by the same providers. Diagnoses for which these patients sought care included benign prostatic hyperplasia, nephrolithiasis, prostate cancer, renal mass, urinary tract infections, postoperative visits and a small number of other miscellaneous, urological chief concerns.

First, we compared clinical efficiency by calculating completion, cancellation and no-show rates as well as cycle time, defined as the amount of time a patient spends in a health care encounter by the Institute for Healthcare Improvement. There was no significant difference in the completion, cancellation or no-show rate (fig. 1), yet the average cycle time of video visits was 24 minutes compared to 80 minutes for clinic visits (fig. 2). For patients, these data confirm that synchronous telehealth reduces the amount of low value time spent interacting with the health care system while finding parking, checking into the clinic and waiting for a clinic room to become available. Instead, a patient’s time is focused on discussing their care with their urologist.

Our findings are supported by the results of a noninferiority, randomized controlled trial for general surgery postoperative video visits. This study demonstrated similar differences in cycle time between virtual and in-person care and prospectively showed that the face time spent with the surgical provider was the same. Prospective evaluations and quality improvement interventions are needed to determine if the reduced cycle times of video visits along with similar completion rates will allow clinics to provide care to more patients on any given day.

When comparing financial metrics our group found that reimbursement rates and patient out-of-pocket expenses incurred through their insurance were similar for video and clinic visits (fig. 3). These findings reflected the state of Michigan’s telehealth parity laws whereby video visits were reimbursed by commercial payers based on billing level. Interestingly, video visits were billed at lower levels with the vast majority (85%) billed as level 3 encounters. Future work must be designed to differentiate whether this reflects a selection of healthier patients for virtual followup or whether providers are not appropriately billing for the complexity of evaluation and decision making that can be done virtually. Collectively, our findings suggest that in addition to improving the patient experience, there is a business case for the implementation of video visits when telehealth parity laws allow for comparable reimbursement.

How has the telehealth landscape changed from the time our group saw these patients? From 2017 to 2019 telehealth parity coverage expanded from 29 states to 36 states and Washington, D.C. During the COVID-19 pandemic there has been a massive expansion of telehealth services due to changes
Endogenous Effects of Leptin on Leydig Stem Cell Differentiation Specific to Body Mass Index

Leptin's effects in the hypothalamus have been well studied, but can leptin also function in downstream sites of the HPG axis and affect fertility and testosterone production? Leptin receptors have been identified in testicular tissue including on Leydig cells, raising the possibility of a full circle connection between obesity, the development of leptin resistance and infertility. As described earlier, testicular adult Leydig cells are essential for reproductive function as they synthesize and release testosterone. The growth and differentiation of adult Leydig cells can be affected by paracrine factors released by Sertoli cells and peritubular myoid cells, which comprise the testicular microenvironment. In our previous study we demonstrated that leptin was an important paracrine factor secreted by Sertoli cells that promotes Leydig stem cell differentiation and subsequent testosterone production via its upstream regulation of the hypothalamic pituitary testicular axis (DHH) signaling. DHH, a protein secreted by Sertoli cells, has been identified as crucial component of the DHH signaling pathway that commits stem cells to the Leydig cell lineage. In our award winning presentation we aimed to evaluate the interplay between leptin and BMI on impacting the differentiation of Leydig stem cells. We hypothesized that leptin has distinct endogenous effects on Leydig stem cell differentiation that are specific to patient BMI.

In our study a total of 13 men with testicular failure underwent testicular biopsies to perform sperm retrieval. These men were categorized based on their BMI as lean (less than 20), normal (20–30) or obese (greater than 30 kg/m²). The testicular tissue was extracted and processed for cell isolation, expansion and characterization. Further experiments were conducted to study if and how Leptin could differentially modulate Leydig stem cell transformation to adult Leydig cells and overall testosterone levels with respect to patient BMI.

Our results demonstrated that in the lean BMI population increasing leptin doses correlated with increased Leydig stem cell differentiation in a linear fashion. In the normal BMI population there was a bell shaped pattern wherein administering low doses of leptin was associated with increased Leydig stem cell differentiation. In the obese BMI population there was an inverted bell shaped distribution between leptin dose and Leydig stem cell differentiation. Furthermore, in the normal BMI population, flow cytometry and immunostaining results showed an increase in the adult Leydig cell population and DHH signaling in the presence of low doses of leptin. These patterns were not consistent in the lean or obese populations.

Overall, our results showed that BMI and leptin signaling have critical influence in impacting Leydig stem cell differentiation. These findings suggest the future potential use of leptin as a personalized therapy for inducing Leydig stem cell differentiation and overcoming low testosterone levels. Further studies are necessary to identify potential therapeutic effects of leptin treatment in improving fertility in the setting of leptin resistance and obesity.

Madhumita Parmar, BS
Himanshu Arora, PhD

Miami, Florida

Infertility affects 10% to 15% of couples worldwide, unrelenting in its presence as a significant global health burden. Up to 50% of infertility cases are related to male factors. Various contributors including genetic predisposition, life-style behaviors and environmental influences are responsible for optimal male reproductive health.

Fundamental to understanding how these factors influence male reproductive function is the hypothalamic-pituitary-gonadal (HPG) axis. The HPG axis is a regulatory framework that responds to positive and negative feedback signals to modulate fertility and testosterone production. The system originates in the hypothalamus, which releases gonadotropin releasing hormone (GnRH) to stimulate the pituitary to release luteinizing hormone (LH) and follicle stimulating hormone (FSH). LH and FSH exert downstream effects on 2 cell types in the testes, Sertoli and Leydig cells. Sertoli cells under the regulation of FSH are responsible for sperm production. Leydig cells with stimulation from LH produce testosterone, the primary male sex hormone. Testosterone exerts negative feedback on the hypothalamus and pituitary to maintain control of the serum testosterone level.

Insult to any point along the HPG axis can result in problems with fertility. Obesity has been found as a significant disruptor of the HPG axis and consequently decreases spermatogenesis and fertility. Studies have shown that increased body mass index (BMI) is associated with decreased testosterone levels and sperm parameters. Several mechanisms have been proposed for the androgen insufficiency and reduced reproductive function in obese men including hyperestrogenemia, insulin resistance, sleep apnea and leptin dysregulation.

Leptin is a protein, mainly secreted by adipocytes, that plays an important role in energy homeostasis, neuroendocrine processes, immune function, and reproduction. Specifically, leptin acts via hypothalamic mediators to decrease food intake and increase energy expenditure, thereby regulating body weight. As leptin is secreted by adipocytes, obese individuals have higher levels of leptin. Paradoxically, increased leptin does not always translate to increased energy expenditure and decreased food intake. Obesity has the potential to induce a functional leptin resistance, negating the normal function of leptin.

Telehealth is here to stay. We cannot simply return to a pre-pandemic status quo when technology may allow us to mitigate issues around access to specialty care, health care disparities and expected workforce shortages. Given our field’s historical tendency to innovate and embrace new technologies, urologists and the American Urological Association are uniquely positioned to help design the future of health care delivery. This redesign is happening right now, and success will require 2 vigorous and simultaneous efforts.

1. Advocacy to ensure telehealth use is accessible to all and financially sustainable.
2. Research to determine when, where and how virtual care can best serve our patients.

Parents of patients with hypospadias face an irreversible choice that has potentially lifelong consequences. They must consider the tradeoffs of possible cosmetic and functional improvement of the child’s penis considering the potential for postoperative complications that may require reoperation. A recent systematic review found that a significant proportion of parents who elected hypospadias surgery for their young child experience decisional regret (DR).\(^1\) Shared decision making (SDM) addresses DR by clarifying modifiable factors in decision making and enabling patients and physicians to use a bidirectional flow of information. Decision aids (DAs) facilitate SDM between families and physicians by providing decision support, thereby improving decision quality. DAs may address unresolved decisional needs by providing information, realigning expectations of outcomes, clarifying values and augmenting skills in decision making.

SDM within the pediatric setting is unique as a parent/caregiver typically acts as a proxy for the child during the decision making process.\(^2\) Proxy decision making in pediatrics is complicated, because children’s developmental capacities increase over time and their changing biology leads to greater potential for long-term risks and benefits from medical care. Although parent preferences for the degree of participation vary, most are interested in sharing decisions with providers. Pediatric SDM is particularly relevant to the management of patients with hypospadias because the ratio of benefit to harm with surgery is “preference sensitive” and varies with the severity of hypospadias and associated penile curvature.

The concept of a SDM model in hypospadias surgery represents a major paradigm shift from the traditional approach in which the surgeon makes a treatment recommendation based on their knowledge of surgeon determined outcomes (e.g., anatomical results, complications, etc.). Although these traditional measures of success are important to ensure safety of surgical procedures, they lack the perspective of the parents who make decisions regarding hypospadias repair. Clarifying parental values/preferences, providing high quality information to educate families and screening for parental decisional conflict (DC) may be valuable strategies to minimize DR after hypospadias repair, an important parent centered outcome. A hypospadias specific DA is an innovative

\(^{1}\) Chan, MD, MPH, Indianapolis, Indiana

\(^{2}\) Figure 1.

\(^{3}\) Figure 2.
and optimal way to address these concerns, reduce DR and improve satisfaction with the decision. To our knowledge this is the first DA being developed specifically for a pediatric urology condition.

Our multidisciplinary team completed an extensive qualitative assessment to explore parent informational needs and preferences/priorities for decision making regarding hypospadias surgery. In addition, we conducted focus groups with parents and pediatric providers, engaging them in the codesign of a hypospadias DA prototype using a human centered design approach. Participants created user friendly, interactive DA prototypes with 24/7 availability that had 3 key functions in common, those being to provide accurate, customizable, educational content about hypospadias, to connect parents to each other and to engage them in a decision making activity (fig. 1). They suggested that the DA might be used at home, work, daycare or the doctor’s office. Key educational content included a multimedia overview of hypospadias and goals of hypospadias surgery with illustrations, photos, 3D models, videos and/or statistics to suit a variety of learning styles. They also recommended an illustrated severity scale with customizable information based on the degree of hypospadias severity, a summary of the pros/cons of surgery and a review of postoperative care/recovery to share with family members and childcare providers. Finally, they suggested parent testimonials about surgical decision making and the day-of-surgery experience.

Next, we conducted a collaborative design and prototyping session to establish key features and requirements and created a content map visualizing this work (fig. 2). This culminated in the creation of our hypospadias DA, called the Hypospadias Homepage. Our work with parents also indicated that they wished for the DA to be user-friendly, interactive and available 24/7. Therefore, the Hypospadias Homepage was designed as an online tool containing several modules. The modules included general hypospadias information including an illustrated severity scale, a storyboard illustrating the basic steps of hypospadias surgery and possible risks of the procedure (ie long-term complications icon array), frequently asked questions about surgery and recovery, 2 values clarification exercises including a printable handout to share with their provider, and provider and parent testimonial videos about the condition, the decision making process and the day-of-surgery experience (fig. 3). These modules address 3 key goals of decision aids that are outlined in the International Patient Decision Aid Standards collaboration checklist, including providing facts about a condition, helping people clarify their values and helping people share their values with their health care provider.

The Hypospadias Homepage has gone through 2 initial rounds of reviews/edits by health care providers. We are currently conducting acceptability and usability testing of the DA with parents of patients with hypospadias before launching a pilot test in the clinical setting. In the future we plan for a randomized controlled trial comparing parent centered outcomes such as hypospadias knowledge, DC and DR in parents who receive “regular care” vs those who view the DA. We are excited to introduce an evidence-based, parent centered tool for pediatric urologists and parents to improve the care of patients with hypospadias in the future.

**INDICATION**
LYNPARZA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.

**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATIONS**
There are no contraindications for LYNPARZA.

**WARNINGS AND PRECAUTIONS**

**Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML):** Occurred in <1.5% of patients exposed to LYNPARZA monotherapy, and the majority of events had a fatal outcome. The duration of therapy in patients who developed secondary MDS/AML varied from <6 months to >2 years. All of these patients had previous chemotherapy with platinum agents and/or other DNA-damaging agents, including radiotherapy, and some also had a history of more than one primary malignancy or of bone marrow dysplasia.

Do not start LYNPARZA until patients have recovered from hematological toxicity caused by previous chemotherapy (≤Grade 1). Monitor complete blood count for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities, interrupt LYNPARZA and monitor blood count weekly until recovery.

If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. Discontinue LYNPARZA if MDS/AML is confirmed.

**Pneumonitis:** Occurred in <1% of patients exposed to LYNPARZA, and some cases were fatal. If patients present with new or worsening respiratory symptoms such as dyspnea, cough, and fever, or a radiological abnormality occurs, interrupt LYNPARZA treatment and initiate prompt investigation. Discontinue LYNPARZA if pneumonitis is confirmed and treat patient appropriately.

**Embryo-Fetal Toxicity:** Based on its mechanism of action and findings in animals, LYNPARZA can cause fetal harm. A pregnancy test is recommended for females of reproductive potential prior to initiating treatment.

**Females**
Advis e females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months following the last dose.

**Males**
Advis e male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of LYNPARZA and to not donate sperm during this time.

**Venous Thromboembolic Events:** Including pulmonary embolism, occurred in 7% of patients with metastatic castration-resistant prostate cancer who received LYNPARZA plus androgen deprivation therapy (ADT) compared to 3.1% of patients receiving enzalutamide or abiraterone plus ADT in the PROfound study. Patients receiving LYNPARZA and ADT had a 6% incidence of pulmonary embolism compared to 0.8% of patients treated with ADT plus either enzalutamide or abiraterone. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism, and treat as medically appropriate, which may include long-term anticoagulation as clinically indicated.

**ADVERSE REACTIONS—HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer**
Most common adverse reactions (Grades 1-4) in ≥10% of patients in clinical trials of LYNPARZA for PROfound were: anemia (46%), fatigue (including asthenia) (41%), nausea (41%), decreased appetite (30%), diarrhea (21%), vomiting (18%), thrombocytopenia (12%), cough (11%), and dyspnea (10%).

**DRUG INTERACTIONS**

**Anticancer Agents:** Clinical studies of LYNPARZA with other myelosuppressive anticancer agents, including DNA-damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.

**CYP3A Inhibitors:** Avoid coadministration of strong or moderate CYP3A inhibitors when using LYNPARZA. If a strong or moderate CYP3A inhibitor must be coadministered, reduce the dose of LYNPARZA. Advise patients to avoid grapefruit, grapefruit juice, Seville oranges, and Seville orange juice during LYNPARZA treatment.

**CYP3A Inducers:** Avoid coadministration of strong or moderate CYP3A inducers when using LYNPARZA.

**USE IN SPECIFIC POPULATIONS**

**Lactation:** No data are available regarding the presence of olaparib in human milk, its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in the breastfed infant, advise a lactating woman not to breastfeed during treatment with LYNPARZA and for 1 month after receiving the final dose.

**Pediatric Use:** The safety and efficacy of LYNPARZA have not been established in pediatric patients.
**Among men with BRCA1/2- or ATM-mutated mCRPC following progression on enzalutamide or abiraterone**

**LYNPARZA more than doubled median rPFS vs retreatment with enzalutamide or abiraterone**¹,⁷

**TRIAL DESIGN**¹,⁷

- The PROfound trial was a prospective, multicenter, randomized, open-label, phase 3 trial of LYNPARZA in patients with HRRm mCRPC
- Key eligibility criteria: Metastatic castration-resistant prostate cancer; progression on prior enzalutamide or abiraterone treatment for metastatic prostate cancer and/or CRPC; a tumor mutation in at least 1 of 15 genes* involved in the HRR pathway
- Patients were divided by mutation: **BRCA1/2** or **ATM** gene mutation (Cohort A [n=245]†) and other HRR gene mutations (Cohort B [n=142]‡), and randomization was stratified by prior receipt of taxane chemotherapy and presence of measurable disease by RECIST 1.1
- Each cohort was randomized 2:1 to receive LYNPARZA (tablets, 300 mg per dose, twice daily) or an active comparator (retreatment with investigator’s choice of enzalutamide or abiraterone)

¹HRR gene mutations (BRCA1, BRCA2, ATM, BARD1, BRIPI, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and/or RAD54L) were identified by tissue-based testing using the Foundation Medicine FoundationOne™ clinical trial HRR assay performed at a central laboratory. No patients were enrolled who had mutations in 2 of the 15 prespecified HRR genes: FANCL and RAD51C.

²Patients with co-mutations (BRCA1, BRCA2, or ATM plus a Cohort B gene) were assigned to Cohort A.

³All patients received a GnRH analog or had prior bilateral orchiectomy.

⁴BARD1, BRIPI, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or RAD54L.

Although patients with PPP2R2A gene mutations were enrolled in the trial, LYNPARZA is not indicated for the treatment of patients with this gene mutation due to unfavorable risk-benefit ratio.

**PRIMARY ENDPOINT: RADIOLOGICAL PROGRESSION-FREE SURVIVAL (rPFS)**¹,⁷

![Graph showing rPFS results](image-url)

- LYNPARZA median rPFS (95% CI: 6.2-9.3) vs 3.6 months for enzalutamide or abiraterone (95% CI: 1.9-3.7)

- **7.4 months**

- **>2X median rPFS**

- 66% relative risk reduction of disease progression or death

- HR=0.34, 95% CI: 0.25-0.47, P<0.0001

**EXPLORE THE DATA, including secondary endpoints, and testing recommendations at LYNPARZAprchcp.com**

**Number of patients at risk**

<table>
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<th>LYNPARZA</th>
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<th>116</th>
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<tr>
<td>Retreatment with enzalutamide or abiraterone</td>
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<td>79</td>
<td>47</td>
<td>44</td>
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**IMPORTANT SAFETY INFORMATION (CONT’D)**

**USE IN SPECIFIC POPULATIONS (CONT’D)**

- **Hepatic Impairment:** No adjustment to the starting dose is required in patients with mild or moderate hepatic impairment (Child-Pugh classification A and B). There are no data in patients with severe hepatic impairment (Child-Pugh classification C).
- **Renal Impairment:** No dosage modification is recommended in patients with mild renal impairment (CLcr 51-80 mL/min estimated by Cockcroft-Gault). In patients with moderate renal impairment (CLcr 31-50 mL/min), reduce the dose of LYNPARZA to 200 mg twice daily. There are no data in patients with severe renal impairment or end-stage renal disease (CLcr ≤30 mL/min).

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

**Please see accompanying Brief Summary of Prescribing Information on the following pages.**

**References:**
**WARNINGS AND PRECAUTIONS**

None.

**CONTRAINDICATIONS**

Pharmacology (12.3) in the full Prescribing Information.

**Dosage Modifications for Renal Impairment**

After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the Lynparza dose taken prior to initiating the CYP3A inhibitor.

**Dosage Modifications for Concomitant Use with Strong or Moderate CYP3A Inhibitors**

If concomitant use cannot be avoided, reduce Lynparza dosage to:

- **HRR gene-mutated metastatic castration-resistant prostate cancer**

Patients receiving Lynparza for mCRPC should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

If a patient misses a dose of Lynparza, instruct patient to take their next dose at its scheduled time. Instruct patients to swallow tablets whole. Do not chew, crush, dissolve, or divide tablet.

**Recommended Dosage**

The recommended dosage of Lynparza is 300 mg taken orally twice daily, with or without food.

If a patient misses a dose of Lynparza, instruct patient to take their next dose at its scheduled time. Do not chew, crush, dissolve, or divide tablet.

**DRUG INTERACTIONS**

Coadministration of strong or moderate CYP3A inhibitors. If the strong or moderate inhibitor must be coadministered, reduce the dose of Lynparza (2.5) in the full Prescribing Information.

**Effect of Other Drugs on Lynparza**

Concomitant use with strong or moderate CYP3A inducers can decrease olaparib exposure, which may reduce Lynparza efficacy (see [Clinical Pharmacology (12.3) in the full Prescribing Information]). Avoid coadministration of strong or moderate CYP3A inducers.

**Use in SPECIFIC POPULATIONS**

**Pregnancy**

Risk Summary

Based on findings in animals and its mechanism of action (see [Clinical Pharmacology (12.3) in the full Prescribing Information]), Lynparza can cause fetal harm when administered to pregnant women. The estimated risk of major birth defects is 2-4%, and the risk for spontaneous abortion is approximately 12-20% in clinically recognized pregnancies.

**Animals**

In a fertility and early embryonic development study in female rats, olaparib was administered orally on gestation days 6 to 17. Administration of olaparib resulted in increased postimplantation loss at a dose level of 15 mg/kg/day (with maternal systemic exposures approximately 7% of the human exposure (AUChuman)). At the recommended dose for humans, olaparib exposure in animals was <1% of the human exposure.

**Amniotic Fluid**

In an embryo-fetal development study, pregnant rats received oral doses of 0.05 or 0.5 mg/kg/day olaparib during the period of organogenesis. A dose of 0.5 mg/kg/day (with maternal systemic exposures approximately 0.18% of human exposure (AUChuman)) at the recommended dose) caused embryo-fetal toxicities including increased post-implantation loss and major malformations of the eyes (anophthalmia, microphthalmia), vertebrae (vertebral fusions, ribs, and limbs) and other findings in the vertebral/bone, genital, lung, heart, thymus, liver, adrenal, and umbilical artery. Some findings noted above in the eyes, heart, and renal were observed at a dose of 0.05 mg/kg/day-olaparib at lower incidence.

**Lactation**

Risk Summary

No data are available regarding the presence of olaparib in human milk, or on its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in nursing infants from Lynparza, advise women not to breastfeed during treatment with Lynparza and for at least 6 months following the last dose.

**Male and Female Reproductive Potential**

**Pregnancy Testing**

Recommend pregnancy testing for females of reproductive potential prior to initiating treatment with Lynparza.

**Contraception**

Females

Lynparza can cause fetal harm when administered to a pregnant woman (see [Use in Specific Populations (8.8) in the full Prescribing Information]). Advise female patients of the potential hazard to the fetus and the potential risk for loss of the pregnancy.

**Males**

Based on findings in genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential who are pregnant to use effective contraception during treatment with Lynparza and for at least 6 months following the last dose.

**Geriatric Use**

Of the 2331 patients with advanced solid tumors who received Lynparza tablets 300 mg twice daily, 66 (3%) patients were aged ≥75 years, and this included 37 (6%) patients who were aged ≥75 years. Seven (0.3%) patients were aged ≥85 years. (see [Adverse Reactions (6.1) in the full Prescribing Information]) 21 of 530 patients with advanced solid tumors who received Lynparza tablets 300 mg orally twice daily in combination with bevacizumab, 204 (38%) patients were aged ≥65 years, 58 (11%) patients were aged ≥75 years, and 2 (0.4%) patients were aged ≥85 years. (see [Adverse Reactions (6.1) in the full Prescribing Information]). No overall differences in the safety or effectiveness of Lynparza were observed between these patients and younger patients.

**Renal Impairment**

No dosage adjustment is recommended in patients with mild renal impairment (Clcr 31-50 mL/min). Lynparza dosage to 200 mg twice daily in patients with moderate renal impairment (Clcr 31 to 50 mL/min) (see [Clinical Pharmacology (12.3) in the full Prescribing Information]). 10 of 530 patients with advanced solid tumors who received Lynparza tablets 300 mg orally twice daily in combination with bevacizumab, 204 (38%) patients were aged ≥65 years, 58 (11%) patients were aged ≥75 years, and 2 (0.4%) patients were aged ≥85 years. (see [Adverse Reactions (6.1) in the full Prescribing Information]). No overall differences in the safety or effectiveness of Lynparza were observed between these patients and younger patients.

**Hepatic Impairment**

No adjustment to the starting dose is required in patients with mild or moderate hepatic impairment (Child-Pugh A classification and B). 10 of 530 patients with advanced solid tumors who received Lynparza tablets 300 mg orally twice daily in combination with bevacizumab, 204 (38%) patients were aged ≥65 years, 58 (11%) patients were aged ≥75 years, and 2 (0.4%) patients were aged ≥85 years. (see [Adverse Reactions (6.1) in the full Prescribing Information]). 10 of 530 patients with advanced solid tumors who received Lynparza tablets 300 mg orally twice daily in combination with bevacizumab, 204 (38%) patients were aged ≥65 years, 58 (11%) patients were aged ≥75 years, and 2 (0.4%) patients were aged ≥85 years. (see [Adverse Reactions (6.1) in the full Prescribing Information]). No overall differences in the safety or effectiveness of Lynparza were observed between these patients and younger patients.

**DRUG INTERACTIONS**

Use with Anticancer Agents

Clinical laboratories or drug interaction studies with other myelosuppressive anticancer agents, including DNA damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.

**Indication Biomarker Sample type**

<table>
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<tr>
<th>Indication</th>
<th>Biomarker</th>
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<td>Venous Thromboembolic Events</td>
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Radioproteomic Analysis as a Predictor of Renal Tumor Histopathology

Jorge Daza, MD Ketan Badani, MD

New York, New York

Small renal masses (SRMs) are defined as renal tumors that measure 4 cm or less in diameter. The standard of care is partial nephrectomy. However, 30.3% and 27.1% of 2 cm or smaller and 4 cm SRMs, respectively, turn out to be benign tumors. Cancer specific survival (CSS) reported on surgically treated clear cell (cc), papillary (p) and chromophobe (ch) renal cell carcinoma (RCC) tumors is 71%, 91% and 88%, respectively, at 5 years. Likewise, CSS at 20 years for ccRCC, pRCC and chRCC tumors is 52%, 83% and 81%, respectively. In this context, histological subtypes play an important role in the decision making process regarding the treatment of these cases.

SRMs have a demonstrated growth rate of 0.22 cm per year and a metastatic progression rate ranging from 1% to 6%. Therefore, alternative approaches including surveillance have been proposed for SRMs, predominantly in patients who are elderly and/or comorbid. However, this is just a selected group of patients, and the rate of overtreatment in the remaining cases is of great concern. There is currently a lack of understanding of the underlying biology within the tumor microenvironment (TME) of SRMs and the potential role it may play in the course of the disease. Some of these differences in the TME might be closely related to clinical tumor characteristics such as histological subtype and grade. In this context, renal biopsy is the method currently used to evaluate preoperatively SRMs. However, the reported negative predictive value is 68%.

Moreover, the rate of Clavien-Dindo 2 or greater complications is 2%. Since cancer related inflammatory response is induced by the stage of the disease, profiling such response could predict tumor characteristics that at the moment can only be assessed by biopsy derived tumor tissue.

Furthermore, advanced imaging techniques are also capable of evaluating changes within the tumor structures such as perfusion changes mediated by neo-angiogenesis induced by different inflammation related molecules. We consider that a radioproteomic analysis may be an effective approach to identify those less aggressive cases that will benefit from a more conservative approach and will have the added benefit of profiling the antitumor response.

Blood (19) and blood matched urine samples (11) were obtained from patients with SRMs the same day of surgery right before procedure initiation. We used a panel of 92 inflammation related markers in matched serum and urine supernatant. Proteins were detected through matched paired antibodies, coupled to unique, partially complementary oligonucleotides and measured by qualitative real-time polymerase chain reaction. This DNA coupled method provides specificity, excluding any antibody cross-reactivity. Multiparametric (mp) magnetic resonance imaging scans (MRIs) were done during the preoperative evaluation of each case in 13 patients from whom we collected matched blood and urine samples. All patients underwent 1.5 T MRIs. Conventional MRI sequences included axial gradient echo T1 weighted images, T2 weighted images with and without fat suppression. Diffusion weighted imaging sequences (DWI) were performed with 16 b-values for estimating intravoxel incoherent model (IVIM) diffusion parameters. For the dynamic contrast-enhanced sequences (DCE), intravenous administration of Gadobutrol (0.1 mmol/kg) was performed. Apparent diffusion coefficient (ADC) values were estimated as a mono-exponential fit over signal intensity values over all 9 b-values. IVIM analysis was performed on the MATLAB platform (version R201b, MathWorks, Natick, Massachusetts). Diffusion coefficient (D), perfusion coefficient (D*) and perfusion fraction (PF) were calculated in tumor volume using the IVIM bio-exponential Bayesian fit. The analysis was performed by 2 observers in consensus. Unsupervised clustering analysis of inflammatory markers in urine showed the presence of 2 clusters, clusters 1 (noninflammatory) and 2 (inflammatory, fig. 1). One-sided Fisher’s exact test revealed a statistically significant difference in

![Figure 1. Unsupervised clustering analysis of inflammatory markers in urine.](image)

![Figure 2. Differential protein expression analysis between described clusters 1 and 2.](image)
the proportion of ccRCC and non-ccRCC cases between signatures (p=0.0455). Differential protein expression analysis between described clusters 1 and 2 showed significant upregulation of inflammatory proteins in samples from patients with ccRCC compared to non-ccRCC cases (fig. 2). Correlative analysis of mpMRI radiomics and Olink proteomics reveals a ccRCC signature associated with inflammation and mpMRI coefficients. A significant positive correlation was found between EN.RAGE and ADC, PF and D. PF also had a significant positive correlation with CCL23 (fig. 3). EN.RAGE is overexpressed in myeloid derived immune cells, neutrophils and macrophages and is associated with worse prognosis in hepatocellular carcinoma.4 On the other hand, CCL23 promotes recruitment of resting T lymphocytes and monocytes, inhibits the proliferation of myeloid progenitor cells and induces angiogenesis.5 Collectively, the data suggest broad effects on the early immune landscape of SRMs that can distinguish ccRCC tumors as effectively as renal biopsies. Detailed analysis of the inflammatory milieu during early stage ccRCC may identify novel targets for immunotherapies for more advanced stages of disease.

In summary, we reported 2 protein clusters that distinguish histological subtypes between ccRCC vs non-ccRCC. Moreover, we have also described an mpMRI protocol that correlates with expression of proinflammatory biomarkers in urine and may reflect changes in the tumor microenvironment without the need of renal biopsies. These findings need further validation with tumor tissue and a larger cohort of patients. While we studied inflammatory related markers in serum, our analyses did not reveal any significant clusters that could distinguish between histological subtypes. This approach may provide a novel, noninvasive strategy to identify prognostic and diagnostic biomarkers in the urine that predict malignant tumors that may require surgical therapy, benign or indolent tumors that could be treated less aggressively, and a profile of the tumor microenvironment of SRMs. Future studies directly on tumor tissue where matched samples of urine and plasma are available are needed to validate our findings.

AUA 2020 Virtual Science Best Poster winner.


Defective Cell Adaptation Determines Response to Androgen Deprivation Therapy

Niall Corcoran, PhD, FRACS(Urol)
Parkville, Victoria, Australia

The therapeutic effect of androgen receptor targeting agents on primary prostate cancer is quite variable, but complete tumor regression is uncommon.1 To gain insights into what factors are important in determining response, we comprehensively analyzed pre-treatment and posttreatment tumor specimens from a neoadjuvant phase II study of profound androgen signalling blockade (fig. 1). Men deemed to be at high risk of recurrence after radical prostatectomy based on their tumor grade, clinical stage and/or serum prostate specific antigen (PSA) were treated with a combination of degarelix (a luteinizing hormone releasing hormone antagonist), abiraterone (an androgen synthesis inhibitor), bicalutamide (an androgen receptor antagonist) and prednisolone for 24 weeks before proceeding to surgery.

Although every patient experienced a significant biochemical response with serum PSA falling by more than 95% the pathological response was much more variable with 3 distinct patterns seen.

Figure 1. Samples used in analysis.

A quarter of the patients were responders, defined as complete pathological response or minimal
Defective Cell Adaption and ADT

Continued from page 20

residual disease (less than 0.1 cc of residual tumor and no Gleason pattern 4/5) with a similar number of nonresponders (high volume residual tumors with no histological evidence of tumor regression). The remaining patients were partial responders with residual tumors greater than 0.1 cc or with persistent high grade elements but with histological evidence of tumor involution. There was no significant association between pretreatment clinical and pathological features and extent of tumor response.

In patients who develop progressive castration resistant prostate cancer, reactivation of androgen receptor signaling through a number of mechanisms (eg androgen receptor gene amplification or mutation, enhanced or alternative signalling androgen synthetic pathways, emergence of constitutively active receptor splice variants etc) is a significant driver of tumor progression. However, initial investigations demonstrated that these were not present pretreatment in the nonresponders nor in persistent residual tumors, suggesting that other mechanisms are at play.

To investigate what these mechanisms might be we performed a genome-wide screen of genes upregulated in residual tumors compared to pretreatment biopsy specimens as well as an untreated cohort of men with similar high risk characteristics. We found significant upregulation of genes involved in epithelial mesenchymal transition (EMT, a type of cellular reprogramming that is associated with resistance to apoptosis in the face of increased cellular stress) in residual tumors but not in castration resistant samples. Interestingly, these changes were also observed in persistent benign prostate epithelium, suggesting it may be a universal mechanism of cell survival following acute androgen receptor signalling inhibition.

Genomic studies have revealed that many primary prostate cancers are not made up of a single cell clone but are more commonly a mix of different cell populations (clonal and subclonal) that harbor distinct DNA aberrations. A potential explanation for tumor cell persistence is that treatment selects out inherently resistant cells (eg cancer stem cells), which can then acquire new genomic lesions that allow them to expand and repopulate the tumor mass (fig. 2). To determine how tumor cell populations changed with treatment, we performed whole genome sequencing of pretreatment biopsy and posttreatment residual tumor specimens. We then used high confidence mutations to estimate the number of cell populations in each specimen and tracked how they changed with treatment. Consistent with previous reports we observed intratumoral heterogeneity at the subclonal level in the majority of patients. However, in patients with no treatment response we saw no change in tumor cell population, suggesting that resistance is intrinsic to these cells rather than a selected trait. By contrast, in patients experiencing tumor regression we saw selective depletion of a treatment sensitive population, suggesting the proportion of this population present in the tumor pretreatment determines objective response.

We then focused on genomic aberrations that were present in the pretreatment samples but absent from the resistant ones and identified that deletion of SNAI2, a master regulator of EMT that is consistently upregulated in persistent tumors, cosegregated with regression subclones. We confirmed this using fluorescence in situ hybridization, demonstrating that the proportion of tumor cells with SNAI2 deletion pretreatment determines objective responses observed. Although we focused on SNAI2 deletion it is likely that other mechanisms that inactivate SNAI2 (for example transcriptional repression through gene methylation) or affect other key EMT machinery (for example ZEB2) may be important.

This is a focus of ongoing work.

AUA 2020 Virtual Science Best Poster winner.

Pulse Modulation with Moses Technology Improves Popcorn Laser Lithotripsy

Khurshid Ghani, MD
57%
<1.0mm
1-2mm

22 fiber tip in close proximity to the fragments makes it hard to keep the procedures since the motion of in the renal calyx during dusting employing a popcorn technique laser lithotripsy especially when confer a unique advantage for when working at distance may pulse travels.1 The Moses Distance pulse is split into 2 pulses, creates the optical energy of the laser Technology™ (Lumenis), in which laser lithotripsy such as Moses Pulse modulated holmium:YAG laser system, short pulse (SP) was found to be superior to long pulse lithotripsy. In a previous study of a nonmodulated holmium:YAG laser system, high power settings had the greatest submillimeter fragmentation.3 Since Ho:YAG radiation is readily absorbed in water, pulse modulation in theory may improve efficacy by delivering more photons through the initial vapor tunnel to constantly moving stone fragments during popcorn lithotripsy.

We chose to investigate Ho:YAG pulse modulation’s effect during popcorn laser lithotripsy in an in vitro model on fragment size distribution, and fragment mass dissolved in fluid (initial fragment mass—final dry mass of all sievable fragments). BegoStones were fragmented using a 120 W Ho:YAG laser (P120 Moses, Lumenis) and a 230 µm core Moses fiber introduced through a LithoVue (Boston Scientific) ureteroscope. An 11 mm glass bulb test tube served as our calyceal model. Using SP and MD mode we assessed 20 W (1 J × 20 Hz, 0.5 J × 40 Hz) and 40 W (1 J × 40 Hz, 0.5 J × 80 Hz) settings delivering a 4.8 total kJ for all tests. Using high speed video analysis we studied the laser strike, defined as the number of pulses that struck the stone during 1 second divided by pulse frequency, to see if this might explain differences in outcomes between SP and MD mode.

Our study had several key findings. MD mode resulted in a smaller fragment size distribution for 20 W and 40 W settings except for the high frequency 80 Hz/40 W setting (fig. 1). In particular, for the setting 1 J × 20 Hz, MD resulted in more mass dissolved in fluid and a lower distribution of fragments 2 mm or greater compared to SP (p <0.05, fig. 2). Regardless of pulse mode, higher frequency settings produced fewer large fragments [2 mm or greater] when compared with lower frequency settings of equal power (fig. 1). For the 20 W setting more direct laser strikes occurred when using SP mode, but MD mode was associated with a higher ratio of indirect strikes and total strike rate (fig. 3). Overall, the total laser strike rate was greater for MD than SP at 15% (SP/1 J × 20 Hz) vs 22% (MD/1 J × 20 Hz) and 25% (SP/0.5 J × 80 Hz) vs 31% (MD/0.5 J × 80 Hz). Surprisingly, we discovered that the majority of strikes were indirect. This result was unexpected given previous studies highlighting the importance of laser fiber to stone distance for stone comminution during popcornning.2–4 Despite SP mode producing more direct strikes than MD at 1 J × 20 Hz, it still performed less favorably. This suggests that the indirect strikes occurring when using MD may be more effective than indirect strikes occurring during SP mode (most likely due to its optimization for energy delivered at distance).

While studies have shown pulse modulation can increase stone fragmentation,1–3 there are no studies understanding the efficacy of pulse modulation during popcorn laser lithotripsy. In a previous study of a nonmodulated holmium:YAG laser system, short pulse (SP) was found to be superior to long pulse mode for popcorn lithotripsy, and high power settings had the greatest submillimeter fragmentation.3 Since Ho:YAG radiation is readily absorbed in water, pulse modulation in theory may improve efficacy by delivering more photons through the initial vapor tunnel to constantly moving stone fragments during popcorn lithotripsy.

We chose to investigate Ho:YAG pulse modulation’s effect during popcorn laser lithotripsy in an in vitro calyceal model.

Figure 2. Fragment size distribution for SP and MD at 1 J x 20 Hz after popcorn laser lithotripsy in in vitro calyceal model.

Figure 3. Laser fragmentation strike rate during popcorn laser lithotripsy for 20 W and 40 W settings using SP and MD mode.
Improvements to Popcorn Laser Lithotripsy

Continued from page 22

Our data demonstrate that pulse modulation confers an advantage especially for the lower power 20 W settings when evaluating fragment size distribution. The amount of 2 mm or greater fragments is reduced, a beneficial feature since it is now recognized that these larger fragments are more likely to increase in size and require additional ureteroscopic intervention. Pulse modulation with this lower power setting may also be attractive for limiting heat generation and improving visualization during high power laser lithotripsy.2 Clinical studies are needed to understand if the differences we observed translate to enhanced surgical results. Future work on using distance detecting sensors to optimize fragmentation based on the stone position in relation to the fiber tip could increase direct and indirect strikes and improve outcomes further. For further insight see the full article in the World Journal of Urology.6

Supported by an investigator research grant from Boston Scientific.


CCR8: Novel Therapeutic Candidate Targeting Tregs in Renal Cell Carcinoma Tumor Tissue

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Immunotherapeutic agents (ICIs) are more effective in treating renal cell carcinoma (RCC) than conventional molecular targeted agents. As a result we use them in first line and second line treatment in general practice.1 However, due to the limited efficacy and safety of ICI therapy there is a need to establish the novel cancer immunotherapy. In our previous report, the population of exhausted CD8 T cells and CD4 regulatory T cells (Tregs) upregulated in patients with RCC with the higher tumor grade, clarifying that tumor grade could become a prognostic marker of patients with RCC treated by nivolumab monotherapy.2

CD4 Tregs play an important role in the construction of immune status within the tumor microenvironment, and depletion of Tregs might become a novel strategy to overcome the therapeutic resistance to ICI therapy. Therefore, identification of a specific molecule to tumor tissue infiltrating Tregs (TIL-Tregs) could lead to maximizing the therapeutic effect by preventing the severe inflammatory adverse events induced by systemic depletion of Tregs. The aim of this study is to identify surface molecules specific to TIL-Tregs in patients with RCC and explore the possibility as a therapeutic target using xenograft models.

First, we extracted 4 CD4 populations including Tregs from peripheral blood and tumor tissue of 3 patients with RCC who underwent surgical resection. By RNA sequencing we compared gene expression profiles among 4 populations (fig. 1, a) and identified CCR8 as a specific gene to TIL-Tregs as compared with conventional CD4 T cells in tumor tissues and Tregs in peripheral blood mononuclear cell (PBMC, fig. 1, b). Flowcytometry analysis showed that CCR8 specifically expressed on the surface of TIL-Tregs. In 18 patients with RCC the intensity of CCR8 on CD4 Tregs was the highest compared to CD8 T cells and conventional CD4 T cells (p <0.001, fig. 2, a) and CCR8 co-expressed with FOXP3 on most CD4 Tregs (fig. 2, b).

Second, we tested the therapeutic potential of antibody targeting CCR8, a molecule specific to TIL-Tregs. Through in vitro study we confirmed that the mouse anti-CCR8 therapeutic antibody had both antibody dependent, cell mediated cytotoxicity and neutralizing activity. When the anti-CCR8 antibody was administered to the xenograft model using the mouse colon cancer cell line (CT26), CD4 Tregs in the tumor microenvironment were significantly depleted (fig. 3, a) and IFNg expression of CD8 T cells significantly increased on the tenth day (p <0.001, fig. 3, a). As a result, remarkable tumor shrinkage was achieved (p <0.01) without body weight loss and the serious side effects such as autoimmune disease (fig. 3, a).

Figure 1. Gene expression profile comparison among 4 populations (a) identified CCR8, a specific gene to Tregs in tumor microenvironment as compared with conventional CD4 T cells in tumor tissues and Tregs in PBMC (b).

Figure 2. CCR8 specifically expressed on Tregs in tumor microenvironment. In 18 patients with RCC intensity of CCR8 on CD4 Tregs highest compared to CD8 T cells and conventional CD4 T cells (a) and CCR8 co-expressed with FOXP3 on most CD4 Tregs (b).
Common Nutraceutical Ingredients in Sexual Medicine

Nearly half of American adults use dietary supplements to improve their health, making it paramount for practicing urologists to have some understanding of the nutraceutical landscape. A supplement as defined by the Federal Food, Drug, and Cosmetic Act is a “vitamin; mineral; herb or other botanical; amino acid; dietary substance for use by man to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, extract, or combination of the preceding substances.” Furthermore, supplements are “not intended to treat, diagnose, prevent, or cure diseases” and are therefore prohibited from making such claims. However, not all products adhere to these rules. Perhaps more concerning is that product labeling, ingredient quality control and premarket safety of these nutraceuticals is the sole responsibility of the manufacturer.

Numerous studies have shown that some nutraceuticals contain contaminants like phosphodiesterase-5 inhibitors (PDE5i), anabolic steroids, mold and even heavy metals such as lead. Not only does this undermine the effects of the active ingredients of the supplement, but some can be potentially dangerous for vulnerable patients.

The realm of sexual medicine has seen countless nutraceuticals marketed to enhance erectile function and testosterone levels. Often these products contain more than 1 ingredient. While some of these ingredients have been studied in randomized controlled trials many have not been as rigorously investigated.

Based on retail sales from General Nutrition Corporation™, Google.com™ generated searches and Amazon.com™ queries, there are a number of nutraceuticals that are commonly encountered in the realm of sexual medicine.

Erectile Function Enhancing Supplements

Panax Ginseng. Several randomized controlled trials have demonstrated up to a 60% improvement in subjects’ international index of erectile function (IIEF) in men using panax ginseng compared to placebo. The side effect profile is relatively mild including headache, gastrointestinal upset, rash and constipation. Despite no trial comparing ginseng to PDE5i, ginseng’s favorable side effect profile and low cost led to The Journal of Family Practice recommending this supplement to men with erectile dysfunction (ED).

L-Arginine. L-arginine is commonly used in male health supplements because it is a precursor to nitric oxide (NO). It has a high first pass metabolism in the liver and is converted to ornithine and urea, which renders low doses (less than 3g) ineffective. Several small trials, including a randomized trial of 50 men with ED, showed a significant benefit in erectile function but only at a dose of 5 g. It has a relatively mild side effect including a 10% decrease in systolic and diastolic blood pressure.

Vitamin B6. Vitamin B6 has also been used to treat erectile dysfunction as it plays a critical role in homocysteine regulation. Homocysteine is thought to inhibit NO synthesis. Despite this purported mechanism of action, clinical trials have only shown a benefit in diabetic men concurrently treated with a PDE5i.

Testosterone Boosting Supplements

Zinc. Results of previous investigations regarding the benefits of zinc supplementation are mixed. While early studies suggest zinc deficiency can cause reversible hypogonadism, supplementation to supernormal levels have revealed both positive and negative results. A number of zinc containing products have greater than the upper limit of the recommended daily allowance (RDA). Despite no reported major adverse reactions at RDA levels, increased dosing can lead to zinc toxicity manifesting as copper deficiency, neutropenia and anemia.

Tribulus Terrestris. Tribulus terrestris, a common weed, has been shown to increase testosterone levels in animal studies. A randomized controlled trial showed no benefit in testosterone levels or erections in humans. To date 24 different studies including 7 human studies have shown indeterminate evidence for the use of tribulus in men’s health. While there is no formal trial showing the safety of this ingredient it has been implicated in renal and liver impairment in several subjects and therefore should be used with caution.

Fenugreek. Fenugreek is a unique supplement ingredient that has been reported not only to improve testosterone levels but also to enhance erections. A randomized double blind, placebo controlled trial did show benefit in arousal and orgasm in men taking fenugreek vs placebo but failed to demonstrate changes in testosterone levels. No other trials have examined fenugreek’s effect on IIEF, and several subsequent trials have demonstrated conflicting evidence on fenugreek’s impact on testosterone. While no major adverse events have been reported in clinical trials, there is a case report of venous thromboembolism.

Conclusions

As long as the U.S. Food and Drug Administration allows manufacturers to regulate the ingredients and premarket safety of their products, clinicians should inquire about patient usage of such supplements. While randomized data suggest a benefit for certain ingredients like panax ginseng the effect of other ingredients is less clear. Many supplements contain numerous different ingredients at variables levels (some with understudied safety profiles) and are subject to contamination, clinicians should inform their patients about the potential risks of nutraceuticals in the sexual medicine domain.

1. Clemensha CG, Thaker H and Sampalaski MK. “Testosterone boosting” supplements composition and claims are not supported by the academic literature. World J Mens Health 2020; 38: 115.
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Interestingly, depletion of CD8 and CCR8 T cells counteracts tumor shrinkage, showing that the efficacy of anti-CCR8 antibody is mediated by CD8 T cells (fig. 3, d). Finally, administration of the anti-CCR8 antibody to xenograft model using mouse kidney cancer cell line showed a significant tumor reduction effect as compared with anti-PD-1 antibody and anti-PD-L1 antibody (p <0.05, fig. 4).

Historically, CCR8 was identified as a monocyte chemoattractant and reported having 7 transmembrane domains and express in monocyte, thymus.3 In CD4 Treg cells, CCR8 has been reported to be upregulated as chemokine receptors along with CCR4. CCR8 has been identified as preferentially expressed on TIL-Tregs that exhibit chemotaxis to the CCR8 ligand CCL11 and we confirmed that the expression of CCR8 was significantly higher than that of CCR4 in RCC tumor tissues (data not shown). Some clinical trials revealed that anti-CCR4 antibody depleted Tregs.4 So anti-CCR8 antibody might become a promising novel cancer immunotherapy targeting TIL-Tregs more specifically.

In conclusion, we identified CCR8 as a molecule specific to TIL-Tregs of patients with RCC. Anti-CCR8 therapeutic antibody has been a promising cancer immunotherapy with fewer side effects and higher response.

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**Figure 3.** Antimouse CCR8 antibody showed antitumor effects through CD8+ T cells by depleting intratumoral Tregs. Tumor shrinkage achieved without body weight loss and serious side effects such as autoimmune disease (a). CD4 Tregs were significantly depleted (b) and IFNγ expression of CD8 T cells increased on tenth day (c). Efficacy of anti-CCR8 antibody is mediated by CD8 T cells (d).

**Figure 4.** Antimouse CCR8 antibody showed better antitumor effects than anti-PD-1 and PD-L1 antibody against RCC cell lines.
Metagenomic Analysis of Genitourinary Microbiome of Postmenopausal Women with Recurrent Urinary Tract Infection

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Community acquired urinary tract infection (UTI) is among the most common infections in the world with more than 30% of women experiencing a UTI in their lifetime. When a patient suffers 3 symptomatic UTIs within a year, the condition is defined as recurrent UTI (rUTI). Postmenopausal (PM) women, a rapidly growing and underserved demographic, are severely affected by rUTI with a UTI recurrence rate of approximately 50%. In this population rUTIs can persist for years, reducing quality of life and imposing a significant health care burden. rUTI is most often treated by long-term antibiotic therapy, but development of antibiotic resistance and allergy leave physicians with fewer treatment options after each episodic relapse. Currently, a lack of basic biological knowledge hinders the development of novel therapeutic strategies for the management of rUTI.

The host environment plays a significant role in determining the outcome of infection. The majority of rUTIs develop in women with a history of UTI, suggesting that changes in the genitourinary (GU) environment after UTI predispose women to rUTI. Although much is known about the microbiomes of the gut, skin and mouth, the GU microbiome is poorly understood and has not been characterized in well-controlled cohorts of PM women. The normal GU microbiome present in the urethra, bladder, vagina and perineal regions may be important in maintaining GU tract health. Changes in the GU microbiome after UTI may also predispose PM women to rUTI. To date, the composition and function of the GU microbiome of PM women has not been systematically analyzed. Here, we present a controlled characterization of the genitourinary microbiome in PM women by metagenomic comparison of controlled cross-sectional human cohorts curated to investigate the episodic cycling of infection characteristic of rUTI. The goal of this cross-sectional study was to use deep whole genome metagenomic sequencing (WGMS) to define and characterize the microbial taxonomic and genomic ecology associated with rUTI history.

After IRB approval and patient consent WGMS was performed on clean catch urine from PM women who passed strict inclusion criteria for uncomplicated rUTI (Fig. 1). Women were sorted into cohorts by clinical history of rUTI including “never UTI” (25) with no clinical history of UTI, “remittent rUTI” (25) with history of rUTI and no current UTI, and “relapsed rUTI” (25) with history of rUTI and no current UTI.

Figure 1. Illustration of rUTI infection cycle and cross-sectional cohort design.

Figure 2. Analysis of taxonomic diversity in metagenomic sequencing. Shannon Diversity (A) and Evenness (B) calculated from species detected in taxonomic analysis. Relative abundance of Lactobacillus in never UTI and remittent rUTI patients (C). Relative abundance of Lactobacillus in noninfected patients taking (+) and not taking (−) EHT (D). Pairwise statistical analysis was performed by Wilcoxon rank-sum. Multiple comparison statistical analysis was performed by Kruskal-Wallis nonparametric ANOVA.

▼ Continued on page 28
current symptomatic UTI. DNA was purified from 10 to 20 ml of urine and analyzed by Qubit fluorimetry for purity. WGMS libraries were sequenced on the Illumina NextSeq 500 platform generating an average of 2.6×10^9 nonhuman paired end reads (2×150bp) per sample, which were analyzed with custom bioinformatic pipelines for taxonomic enrichment and functional profiling of the detected metagenomes.

Our analysis identified 373 total microbial species belonging to 162 genera across all samples. Our results indicate that the diversity and evenness of the GU microbiome is similar between “never UTI” and “remittent rUTI” cohorts but reduced in the “relapsed rUTI” cohort (fig. 2, A and B). We observed a relative enrichment of the species Escherichia coli in the relapsed rUTI cohort and of the genera Lactobacillus, a putative protective member of the GU microbiota, in the never UTI cohort. Interestingly, we did not observe a relative enrichment of Lactobacillus in the never UTI cohort relative to the remittent rUTI cohort (fig. 2, C). Interestingly, among women in these 2 cohorts we observed an almost exclusive enrichment of Lactobacillus in women taking estrogen hormone therapy (EHT). Women not taking EHT consistently exhibited low or undetectable levels of Lactobacillus within the GU microbiome (fig. 2, D). Members of the genus Lactobacillus are protective within the cervic vaginal microbiome and may play a similar role in the GU microbiome.4,5 These ongoing analyses significantly advance our understanding of the relationship of the GU microbiome to rUTI pathogenesis and lay the framework for future, targeted research endeavors toward the development of novel, microbiome aware therapeutic options for rUTI in PM women.

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### Risk Factors, Incidence and Timing of Vitamin B12 Deficiency after Urinary Diversion

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The use of ileum for reconstruction of the lower urinary tract has become routine in modern practice, but the risk of vitamin B12 deficiency after bowel resection for urinary diversion remains poorly studied. Vitamin B12 is essential for DNA synthesis and neurologic function and cannot be synthesized by the body. A normal diet contains adequate B12 to prevent deficiency as long as intestinal absorption is not impaired. Intrinsic factor secreted by the stomach binds to dietary B12, and the complex is absorbed primarily but not exclusively in the terminal ileum.1

Resection of a segment of ileum therefore creates potential for impaired absorption of B12, which could lead to systemic deficiency. Earlier studies have estimated a wide range of prevalence of B12 deficiency after urinary diversion from 0% to 34%.1 While most cases of B12 deficiency are asymptomatic, there is the potential for serious symptoms including megaloblastic macrocytic anemia and irreversible neuropathy from funicular myelosis (degeneration of spinal cord white matter). However, reports of symptomatic B12 deficiency resulting from urinary diversion are rare.2 This led our group to reconsider the utility of routine serum B12 monitoring after urinary diversion, by assessing the incidence, timing, and risk factors for B12 deficiency at our institution. Overall we found that B12 deficiency is common after urinary diversion and occurs earlier than previously thought.

With institutional review board approval we reviewed the Duke University Medical Center electronic health record for all patients who underwent cystectomy with urinary diversion between December 1997 and October 2018. Patients under the age of 18 years or with less than 1 year of followup were excluded. Demographics, comorbidities, diversion type and B12 assay results were collected. B12 deficiency was defined as a value under 300 ng/l, which is the level at which we routinely recommend B12 replacement (intramuscular or sublingual) to prevent B12 levels from falling to a dangerous range. A total of 1,228 patients underwent cystectomy with urinary diversion. Of those, 856 (68.7%) had 1-year or more followup with median followup of 16 months [IQR 15–41]. The majority of patients were male (71.4%) and Caucasian (83.5%), with median body mass index (BMI) of 27.1 [IQR 24.1–30.4]. B12 monitoring was performed in 299 patients (34.9%), and B12 deficiency developed in 149 patients (49.8%) at a median time of 10 months [IQR 3–24] after urinary diversion.

The low rate of B12 monitoring was surprising, as this is a routine part of urinary diversion followup in our reconstructive clinic. However, this likely represents the wide variability in practice patterns across different providers and subspecialties. In those who were monitored B12 deficiency was very common (nearly half of patients) and occurred quickly after surgery. As B12 deficiency is generally thought to develop over years as reserves are depleted, this suggests that patients may have had baseline deficiency or low to normal levels and quickly developed deficiency following bowel resection. This finding underscores the importance of B12 monitoring routinely even in the immediate postoperative period. Additionally, preoperative B12 levels could be checked to identify those patients with low or low to normal values and initiate early supplementation.

Those who developed B12 deficiency were younger at time of cystectomy (age 62.5 years vs 66.4, p=0.003) and were more likely to have undergone a continent diversion (19.5% vs 10.7%, p=0.049). Gender, race and BMI did not differ between groups. On univariable analysis younger age decreased the odds of developing B12 deficiency (OR 0.97, 95% CI 0.95–0.99, p=0.002) while continent diversion increased odds of B12 deficiency (OR 2.02, 95% CI 1.06–3.99, p=0.04). On multivariable analysis these relationships were no longer significant but female gender increased the odds of B12 deficiency (OR 2.17, p=0.04). While we did not show a definitive association between continent diversion and B12 deficiency, this association has been shown previously and makes sense due to the increased length of ileum used for orthotopic reconstruction and the use of the terminal ileum for continent catheterizable pouches.4,5 It is unclear why female patients had higher odds of B12 deficiency in this cohort, but this could be explained by dietary or physiological difference influencing baseline B12 levels and therefore risk of deficiency. These risk factors should be considered when determining the timing and frequency of B12 monitoring.

Overall, this study demonstrates that B12 deficiency is common after urinary diversion and can occur quickly after surgery. Selection bias may have played a role as a large proportion of the patients did not have B12 levels monitored, although this is more likely due to variation in provider practice than patient selection. Our standard practice is to monitor B12 levels...
**B12 Deficiency after Urinary Diversion**  

Continued from page 28

... annually, and we have now added baseline B12 levels as part of our preoperative assessment. Based on the findings reported herein, we recommend similar routine B12 monitoring be considered among all patients undergoing urinary diversion. Future studies in this area could address the impact of preoperative B12 supplementation on postoperative B12 deficiency rates, and explore the impact of gender and age on B12 deficiency.  

*AMA 2020 Virtual Science Best Poster winner.*


**N-Terminal Domain Inhibitors of the Androgen Receptor for Prostate Cancer**

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The vast majority of patients with metastatic castration resistant prostate cancer (mCRPC) who are treated with anti-androgens will develop resistance and progress while on therapy. Rising prostate specific antigen (PSA) levels in these patients reveals continued dependence by the tumor on the androgen receptor (AR) pathway. Even with the latest generation of anti-androgens (eg AR-V7).

**Selective NTD AR Inhibition by EPI-7386**

EPI-7386 represents the newest generation of anitens with higher potency and improved metabolic stability relative to the first generation molecules (EPI-002 and its prodrug EPI-506). EPI-7386 demonstrates potent activity in cells expressing full length AR with an IC\textsubscript{50} of approximately 400 nM in the inhibition of AR driven genes. Its in vitro activity represents a twentyfold improvement in potency vs the first generation molecule EPI-002 (fig. 2) and importantly places EPI-7386’s potency now in the same range as current AR inhibitors (“—lutamides”—enzalutamide, apalutamide, darolutamide).

Importantly, EPI-7386 inhibits the full length AR as well as AR splice variants which are resistant to currently approved anti-androgens. In cells expressing full length wild type AR (LNCaP) or those expressing AR-V7 (LNCaP95), EPI-7386 was able to strongly inhibit the AR pathway at the transcriptomic level, with an effect similar to enzalutamide on the full length pathway, and activity on AR-V7 dependent genes on which enzalutamide had no effect. These observations translated into antiproliferative activity in full length AR and AR-V7 driven cell lines.

In castrated mice bearing full length AR driven tumors (LNCaP), full length AR and AR-V7 driven tumors (VCaP, 22Rv1, LNCaP95) or CRPC patient derived xenograft tumors resistant to enzalutamide (HID28) once per day dosing of EPI-7386 markedly decreased tumor growth. The absence of activity of EPI-7386 in the PC-3 model, which does not rely on the AR for its growth, reinforces its on-target activity on AR.

**The Promise of Combined NTD and LBD AR Inhibition**

Additional data suggest a benefit of combining an AR LBD inhibitor with an AR NTD inhibitor in CRPC models. This approach more thoroughly blocks the AR pathway activity and might potentially reduce the chance of developing LBD targeted resistance mechanisms. By analyzing the transcriptomic activity of EPI-7386 combined with enzalutamide in LNCaP cells using RNAseq...

Continued on page 30

![Figure 1: Structure of AR and mechanisms of inhibition.](image1)

![Figure 2: Effect against androgen induced PSA luciferase activity in LNCaP cells.](image2)

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Continued on page 30
broader and deeper inhibition of the AR pathway was demonstrated. Combination therapy translated also into a more robust inhibition of tumor growth in the in vivo VCaP CRPC xenograft model. In this model the combination of enzalutamide with EPI-7386 resulted in consistent tumor regressions observed in all tumors in this treatment group with lower plasma PSA levels compared to the single agents (fig. 3).

**EPI-7386 was Well-Tolerated in Rat and Dog Tox Studies and is Predicted to Achieve High Exposures in Humans**

The projected pharmokinetic (PK) parameters in humans were estimated through a combination of clearance parameters from in vitro assays in mouse, rat, dog and human hepatocytes supplemented with the mean of the in vivo volume of distribution values across nonclinical species. PK profiles of EPI-7386 were simulated along with human C$_{\text{max}}$ and area under the curve (AUC)$_{0-24h}$ at steady state using predicted oral bioavailability (79.4%), predicted clearance (0.275 L/h/kg from hepatocyte CL int, 0.3 (79.4%)), predicted clearance (0.275 using predicted oral bioavailability) with the mean of the in vivo volume of distribution and metabolic stability. Based on these data an optimal biological effect could be observed in patients when EPI-7386 exposures reach levels greater than 300,000 ng•h/ml corresponding to human doses greater than 400 mg per day.

**Summary**

EPI-7386 is a second generation AR NTD inhibitor with excellent potency and metabolic stability. Based on the results of preclinical efficacy models, this agent demonstrates the potential to be developed clinically as a single agent in the setting of anti-androgen clinical resistance as well as in combination therapy with standard of care anti-androgens in earlier stages of the disease. The phase I dose escalation clinical trial of EPI-7386 in men with mCRPC progressing on second generation anti-androgens is currently underway (NCT04421222) and began with a starting oral dose of 200 mg once a day. The study follows a classic 3+3 design with an estimated 18 patients enrolled in the dose escalation part of the study and expansion to 10 additional patients at the recommended phase II dose. The primary objectives of this first in human study are to determine the recommended phase II dose based on the drug safety and exposure profiles and the preliminary antitumor activity (as measured by PSA levels and circulating tumor cells [CTC] count changes). In addition, exploratory molecular characterization of the tumors will be conducted by longitudinally conducted liquid biopsies (ie ARV7 protein expression in CTCs and circulating tumor DNA).

* AUA 2020 Virtual Science Best Poster winner.


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**Exploring Regional Adoption of New Assessment Technologies for Prostate Cancer**

New technologies have been put into practice to help overcome uncertainty in the diagnosis and staging of prostate cancer. For patients with suspected or known prostate cancer, prostate magnetic resonance imaging (MRI) and several tissue based gene expression tests (genomic tests) appear to improve detection and prognostic estimates. By refining assessments of clinical risk, it has been inferred that prostate MRI and genomic testing will also facilitate observational management for suitable patients.

To date, the evidence supporting the clinical value of these tests has largely come from studies performed under optimal conditions such as cohort studies of patients treated at academic institutions and randomized controlled trials.** Less is known about how prostate MRI and genomic testing have become adopted in real-world practice or how their use has impacted clinical decision making. Determining the effectiveness of new technologies is inherently challenging because there are many other factors that can also affect a patient’s decision for treatment vs observational strategies such as active surveillance. These include the patient’s age, comorbidity, personal preference, family history as well as the physician they see or region they live in. Moreover, the decision to obtain a prostate MRI or genomic test itself is complex and is likely in part connected with the inclination of the patient or provider to treat or
pursue observation. In addition, the availability of testing coincides with trends already in motion favoring the rapid uptake of observation for prostate cancer in all patients.

We evaluated the association between a region’s adoption of prostate MRI and genomic testing and changes in observation for prostate cancer. Using administrative claims from Blue Cross Blue Shield, the largest commercial health insurer in the United States, we focused on trends at the Hospital Referral Region (HRR), geographical areas with distinct health care referral patterns that have been defined in the Dartmouth Health Atlas. Among men with a new diagnosis of prostate cancer we identified claims for prostate MRI and commercially available genomic tests marketed for patients with localized prostate cancer. In each 1-year study period we calculated the proportion of patients within each region who received prostate MRI, genomic testing and observation vs treatment for prostate cancer. We also compiled previously defined ecological indicators measured at the HRR level that reflect socioeconomic status such as income, education level, and patterns of prostate cancer screening and treatment.

Although prostate MRI, genomic testing and observation increased overall, use varied significantly by region with some showing decreasing annual rates of observation. In multivariable linear regression models adjusted for regional characteristcs and baseline prostate cancer practices we found that increasing HRR level use of prostate MRI was associated with greater change in the use of observation for prostate cancer. Regional increases in the use of genomic testing were positively correlated with increases in observation for prostate cancer. However, they did not meet the predefined criteria for statistical significance when adjusting for use of prostate MRI and other covariates.

Using a large sample of privately insured patients with prostate cancer we explored regional differences in the use of prostate MRI and genomic testing. Our findings that regional adoption of prostate MRI was associated with change in a region’s overall use of observation are in line with the anticipated outcomes of testing but are framed by several methodological considerations. It is worth emphasizing that the analytic unit in this study was the region and may fail to account for effects at the individual level such as those contributed by cancer characteristics or the findings of testing. Nonetheless, this work can expand efforts to measure the impact of new forms of testing at the population level in light of their expense and potential to intensify the complexity of care.

**Uncovering the Nature of Magnetic Resonance Imaging Invisible Prostate Cancer**

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Prebiopsy multiparametric magnetic resonance imaging (mpMRI) has high test accuracy, validity and reliability for detection of clinically significant prostate cancer. Favorable diagnostic performance characteristics of mpMRI has resulted in refinement of the risk stratification process for suspected cancer and the progressive incorporation of mpMRI into national and international prostate cancer guidelines. Increasing clinical reliance on mpMRI has generated a growing body of research working to characterize the nature of disease that is detected and undetected by this technology. The requirement to understand the types of prostate cancer that are undetected is particularly important if mpMRI is used as a pathway triage tool in which prostate biopsy is omitted in cases of normal or negative scan results. Approximately 10% to 20% of significant prostate cancers are not detected by mpMRI (fig. 1) and the purpose of our study was to characterize the nature of mpMRI invisible disease within the context of the Prostate MR Imaging Study (PROMIS).

PROMIS was a multicenter study that compared performance of mpMRI vs traditional systematic transrectal ultrasound (TRUS) guided biopsy for the diagnosis of clinically significant prostate cancer in men who are biopsy naïve. Each patient underwent 1.5 Tesla (T) mpMRI followed by systematic TRUS-guided biopsy and simultaneous transperineal template mapping (TPM) biopsy (as the reference standard) in which biopsies were taken at 5 mm intervals across the entire prostate. Detected disease was defined as significant cancer on TPM biopsy associated with mpMRI scores of Likert 3-5 while undetected disease was defined as significant cancer on TPM biopsy associated with mpMRI scores of Likert 1-2. Clinically significant cancer was defined using 2 definitions. Definition 1 was defined as overall Gleason score 4+3 or greater of any length or maximum cancer core length (MCCL) of 6 mm or more of any grade, while definition 2 was defined as overall Gleason score 3+4 or greater of any length or MCCL of 4 mm or more of any grade. Prostate specific antigen density (PSAD) was estimated by dividing serum prostate specific antigen (PSA) by mpMRI derived
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prostate volume (using the prolate ellipsoid approach). In this post hoc analysis we compared key pathological differences between significant cancer that was detected by mpMRI, against disease that was undetected by mpMRI using both definitions of clinical significance (fig. 2). We found that 7% (17/230) of men with definition 1 cancer had significant disease undetected by mpMRI, and that 13% (44/331) of men with definition 2 cancer had significant disease undetected by mpMRI. By contrast, traditional TRUS guided biopsy overlooked 52% (119/230) of definition 1 disease and 40% (132/331) of definition 2 disease. Cancer that was not detected by mpMRI had significantly lower overall Gleason scores (p < 0.0001) compared to cancer that was detected by mpMRI (fig. 3). Furthermore, mpMRI undetected tumors had shorter MCCL lengths (median 5 vs 8 mm, p < 0.0001) compared to mpMRI detected disease. No tumors with overall Gleason score greater than 3+4 (Gleason Grade Groups 3–5) or maximum Gleason score greater than 4+3 (Gleason Grade Groups 4–5) were undetected by mpMRI.2

Next, we evaluated the utility of theoretical PSAD thresholds (above which, a biopsy would be indicated) in reducing proportions of significant cancer overlooked by mpMRI. Application of a PSAD threshold of 0.10 ng/ml/ml to negative mpMRI reduced the proportion of men with undetected disease to 3% (6/230) for definition 1 cancer and to 3% (11/331) for definition 2 cancer.2

By capitalizing on the unique opportunity afforded by PROMIS1 we have shown that the proportion of the most important cancers systematically overlooked by 1.5T mpMRI was low (7%).2 At the time of data collection for PROMIS 1.5T was norm magnet strength for mpMRI. However, today 3T mpMRI is more ubiquitous, and as such, true proportions of overlooked cancer on modern MRI machines may be even lower than our estimates. Our analysis has shown that cancer that was undetected by mpMRI was histopathologically less aggressive than detected cancer, and we have recently ratified this finding at the genetic level with a systematic review and bioinformatic analysis in which we demonstrated that mpMRI visible disease is enriched with the molecular, genetic and microenvironmental features of aggressive disease.3 The crucial element missing in this field now is mpMRI phenotype correlated long-term clinical outcomes.4 However, evidence is gradually building, and early reports suggest that mpMRI may have predictive utility in forecasting biochemical recurrence after prostatectomy.5

In the past 1 to 2 years there has been an emerging interest in so-called biparametric magnetic resonance imaging (bpMRI) in which contrast dependent sequences are removed due to perceived lack of necessity.2 In another analysis of the PROMIS data set, it was recently shown that removal of the contrast sequence from prebiopsy bpMRI had almost no effect on the diagnostic accuracy for detection of clinically significant disease.6 However, while mpMRI and bpMRI techniques appear to have similar test characteristics, there are a number of contrast dependent tumors that would be missed (ie bpMRI invisible) if the contrast sequence was omitted. These represent an important avenue for future research, particularly if we move toward using bpMRI as a potential prostate cancer screening tool.

In summary, on a per patient basis few clinically significant prostate cancers are undetected by mpMRI. Our post hoc analysis of PROMIS has demonstrated that prostate cancers undetected by mpMRI are lower in grade and size than detected disease. These findings reinforce the key role that mpMRI plays in risk stratification of men with suspected prostate cancer. As part of this ongoing project, further in-depth analysis of mpMRI invisible disease is underway to enrich our understanding of this important yet elusive disease entity.

AUA 2020 Virtual Science Best Poster winner.◆

Mini vs Standard: The Cost of Percutaneous Nephrolithotomy

Perforation nephrolithotomy (PCNL) has traditionally been the standard of care for staghorn calculi and larger kidney stones greater than 20 mm. The standard PCNL (pPCNL) procedure typically involves a 30Fr dilation through a patient’s flank into the renal collecting system. However, improvements in technology have produced smaller and more powerful instruments that have effectively allowed for smaller PCNL dilation tracts while achieving similar stone removal rates.

The pPCNL dilation for stone removal while effective presented issues with prolong hospitalizations, a small but not insignificant need for blood transfusion and protracted pain particularly when nephrostomy tubes remained. Minipercutaneous nephrolithotomy (mPCNL) is now a consideration for smaller lower pole stones due to its high stone clearance rates compared to retrograde intrarenal surgery or extracorporeal shockwave lithotripsy, but the capability of this procedure for larger stone sizes and types is now being widened and tested.

With the development of smaller lithotripters and advancements in long pulsed and stabilization modes for holmium laser lithotripsy, our team has used mPCNL for a range of kidney stones where a standard dilation may be increasingly traumatic including lower pole renal stones between 10 and 20 mm, di- verticular stones and patients whose postoperative pain may present an issue. The modern mPCNL system uses a single step metal dilator and sheath and was designed for the removal of lower pole stones 0.8 to 1.5 cm. Although different sizes exist for mPCNL dilations, the most popular within the United States is the 16.5/17.5Fr inner/outer diameter reusable single metal dilator and sheath. While a smaller dilation tract has advantages in reducing blood loss, reducing renal trauma and potentially improving post-operative pain, a seldom examined aspect is the financial cost. Additionally, mPCNL may be the first step for urologists who wish to transition from a placement of a postoperative nephrostomy tube to a tubeless procedure with just an indwelling ureteral stent.

Although procedures should be chosen based on best modality to clear stones, it is inevitable that cost may play a role in the type of procedure chosen. Single step balloon dilators and serial dilation with Amplatz renal dilators have been shown to increase cost when compared to reusable metal dilators. In our study we examined all PCNL procedures performed at our standalone ambulatory surgery center in a 6-month period from April to September 2019. All procedures regardless of dilation size were performed in a tubeless fashion with urinary drainage via a single indwelling ureteral stent. Our mPCNL dilation size was 16.5/17.5Fr while our sPCNL dilation size ranged from 24/28 to 30/34Fr. All dual tract procedures and patients needing transfer to hospital were excluded. Patient and stone characteristics as well as disposable costs were compared to cost as much as a mPCNL for a 40 mm partial staghorn is likely to cost as much as a mPCNL for a 10 mm lower pole stone. Our findings suggest that in economic models such as within a surgery center where disposable costs are tallied and subtracted from a renegotiated surgery facility cost, mPCNL is a viable and effective procedure for stones between 10 and 40 mm while having the advantage of lowering disposable costs.

<table>
<thead>
<tr>
<th>Total No.</th>
<th>mPCNL</th>
<th>pPCNL</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age±SD (IQR)</td>
<td>50.42±14.88 (23–71)</td>
<td>59.1±12.72 (27–81)</td>
<td>0.0045</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>13:20</td>
<td>25:34</td>
<td>0.0780</td>
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<tr>
<td>BMI±SD</td>
<td>28.27±5.17 (17–36)</td>
<td>29.81±6.98 (20–48)</td>
<td>0.2750</td>
</tr>
<tr>
<td>cm Skin-to-stone±SD (IQR)</td>
<td>10.23±2.76 (4–16)</td>
<td>10.53±2.64 (5.5–19)</td>
<td>0.1916</td>
</tr>
<tr>
<td>mm Stone burden±SD (IQR)</td>
<td>17.73±7.52 (8–40)</td>
<td>33.38±22.22 (8–130)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Hounsfield Units±SD (IQR)</td>
<td>959±312 (450–1,500)</td>
<td>878±327 (300–1,500)</td>
<td>0.2511</td>
</tr>
<tr>
<td>OR time in mins (IQR)</td>
<td>85.36±15.71 (55–126)</td>
<td>90.38±20.52 (53–134)</td>
<td>0.2290</td>
</tr>
<tr>
<td>Fluoroscopy time in secs (IQR)</td>
<td>86.18±30.09 (50–166)</td>
<td>83.80±39.28 (36–209)</td>
<td>0.7650</td>
</tr>
<tr>
<td>Intracorporeal time in mins (IQR)</td>
<td>37±9.57 (12–60)</td>
<td>41.22±18.96 (12–103)</td>
<td>0.2390</td>
</tr>
<tr>
<td>Treatment time in mins (IQR)</td>
<td>12.22±9.20 (3–68)</td>
<td>14.86±15.90 (1–68)</td>
<td>0.3918</td>
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</table>

**Figure.** Disposbile cost difference between mPCNL and pPCNL.

<table>
<thead>
<tr>
<th>Disposable Cost in U.S. dollars</th>
<th>mPCNL</th>
<th>pPCNL</th>
<th>p Value</th>
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<td>$1,382.42</td>
<td>$1,493.31</td>
<td>*p=0.0003</td>
<td></td>
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<tr>
<td>$1,805.20</td>
<td>$1,716.22</td>
<td>*p=0.0007</td>
<td></td>
</tr>
</tbody>
</table>

**Table.** Demographics, stone characteristics and OR times between mPCNL and sPCNL.

Patient Reported Urinary Tract Infections Affect Quality of Life after Spinal Cord Injury

Accurate diagnosis of urinary tract infections (UTIs) in individuals with spinal cord injury (SCI) and neurogenic bladder is challenging and has resulted in barriers to research in this arena. SCI often results in altered bladder sensation, so patients frequently endorse vague and nonspecific symptoms when a UTI is present. These symptoms may include abdominal pain, increased bladder sensation, or urinary urgency. These complaints in combination with the ubiquitous presence of bacteriuria from catheter use and/or bladder augmentation make it difficult for providers to attribute these symptoms to anything other than a UTI. Therefore, patients are repeatedly told that their symptoms are a result of a UTI and the treatment is antibiotics. It follows that when these individuals experience similar symptoms in the future they have the perception that their illness is a result of their urinary tract, which influences providers and drives therapeutic interventions (ie more antibiotics).

It is important that patients and providers understand that these nonspecific symptoms can be the result of other bodily disruptions or illnesses (ie constipation, dehydration, bladder spasms, bladder stones). In fact, older data suggest that when individuals with SCI believe they have a UTI a full workup will reveal a different etiology in 40% of instances. Therefore, many patient reported UTIs (PRUTIs) may not be true UTIs, but the importance of these symptomatic events should not be overlooked. We believe that more research is needed to better understand PRUTI events if we hope to advance antibiotic stewardship efforts and optimize SCI care and genitourinary quality of life (QOL).

Therefore, we designed this study with the goal of defining the burden of disease individuals with SCI are attributing to their urinary tract by evaluating the association between PRUTIs and quality of life (QOL). We hypothesized that patients who reported more UTIs would report worse QOL.

We used the Neurogenic Bladder Research Group (NBRG) SCI registry (https://www.NBRG.org) for this project. This registry was developed to prospectively study neurogenic bladder related QOL after SCI [ClinicalTrials.gov NCT02616081]. This is an observational registry and all participants completed a robust enrollment interview with a trained study coordinator to collect demographic and clinical data. The frequency of PRUTIs was gathered by participant response to the question, “How many urinary tract infections (bladder or kidney infections) have you had over the past 12 months?” No chart review was conducted to link these episodes to positive urine cultures or specific signs and symptoms because our goal was to understand the effect of patient perceived UTIs on QOL (regardless of whether the UTIs were true infections).

We then used 4 validated QOL questions from the Spinal Cord Injury – Quality of Life (SCI-QOL) questionnaire to determine the association between PRUTI rate and QOL.

The results were striking. We found that an increasing rate of PRUTIs was inversely related to QOL for all 4 questions (see figure). When controlling for confounders such as level of injury, time since injury, bladder management strategy, baseline bladder dysfunction, level of support at home and several other variables, we found that increasing PRUTI rate was independently associated with worse QOL across all 4 QOL items.

Specifically, when comparing individuals with more than 6 PRUTIs in a year to those who reported none, individuals with more than 6 were more likely to limit their daily activities because of a UTI (OR 9.0, 95% CI 8.1–21.2, p <0.001), experience increased skeletal muscle spasms (OR 12.4, 95% CI 7.5–20.6, p <0.001), perceive that a UTI would not go away (OR 30.1, 95% CI 16.0–60.4, p <0.001) and avoid going out in public because of a UTI (OR 7.5, 95% CI 4.2–12.4, p <0.001). We were also fascinated to see that the detrimental effect of PRUTIs on QOL occurred in a dose dependent fashion (see manuscript for data) arguing that any incremental improvement in PRUTI rate can improve patient QOL.

Our findings should be understood in the context of striving to address important health concerns for individuals with SCI. Bladder function specifically has been cited as an important QOL issue by individuals with SCI. This is likely because of the morbidity that often accompanies neurogenic bladder dysfunction after SCI.

Data suggest that as many as 45% of individuals with SCI are hospitalized annually for genitourinary issues, the most common being UTIs. Survey data show that recurrent UTIs are reported by up to 60% of individuals after SCI, 40% of whom concede that these represent a significant health concern. While patient reported “recurrent UTIs” following SCI may

Figure.
not reflect true urinary infections, these “ill” events are arguably still worthy of study for several reasons. First, patient perception influences provider interventions and may result in over diagnosis of UTIs. Second, patient perception drives antibiotic prescribing and use if patients are under the impression that the only solution to their symptoms is antibiotics. Third, patient perception of recurrent UTIs may result in a poorer QOL that gets attributed to the urinary tract.

Our study shows that patient perceived UTIs in individuals with SCI do indeed have a detrimental impact on QOL. Even if these health events are not true UTIs, providers should still aim to diagnose and treat the underlying cause of the presenting symptoms (eg constipation or detrusor overactivity) to improve overall QOL in this population. Only when we better understand true UTIs vs patient perceived UTIs will we be able to effectively address antibiotic overuse and work to find nonantibiotic treatment alternatives for these bothersome symptoms.

**Crossfire: Controversies in Urology—Almost as Good as the Real Thing?**

**Bradley A. Erickson, MD**
Iowa City, Iowa

The debate was lively. The conversation was heated. Tears were shed. But in the end, each of the members of the esteemed panel of reconstructive and oncologic urologists agreed on 2 basic facts. First, robotic technology is here to stay (and will only get better). Second, when able to replicate basic reconstructive principles (sufficient blood supply, tension-free anastomoses, meticulous tissue handling) the robot can be a useful tool when managing difficult reconstructive cases and in some specific cases may even surpass the abilities of traditional open surgery. Here are some of the highlights of our discussion.

There seem to be 3 areas of reconstructive urology in which robotic technology currently offers benefits relative to open surgery, including ureteral reconstruction, bladder neck reconstruction and urological fistula repair. However, the adoption of robotic technology in these areas has been slow, and Dr. John Kelly, a urologic oncologist from University College London, offered the explanation that reconstructive urologists have traditionally lacked an index robotic case with numbers robust enough for easy adoption. Whereas oncologists have been removing prostates robotically for more than 20 years, the reconstructive urologist was unlikely to obtain enough benign ureteral pathology, for example, in a short enough period to comfortably make the transition. It comes as no surprise then that oncologists, and younger reconstructive urologists more familiar with robotic technology from their recent residency are leading the charge in this field. However, Dr. Kelly offered that the mentoring process must still go both ways, with the oncologist offering technical and technical advice and the reconstructionist ensuring that basic reconstructive principles and functional outcomes goals are upheld.

Dr. Daniel Eun, a urologic oncologist from Temple University, is an oncologist who is innovating in the field of benign robotic urological reconstruction. Similar to arguments made about robotic technology for prostatectomy, Dr. Eun stated that improved visualization in difficult to reach and see places (eg under the pubis, behind the bladder) offered by the robot can improve his ability to do innovative and complex ureteral reconstruction. Techniques used and developed by Dr. Eun and his team at Temple include robotic appendiceal interpositions (for right sided distal ureteral pathology), robotic buccal onlay ureteroplasties (fig 1) and robotic nonanastomising side-to-side anastomoses for distal ureteral reimplants.12 Notably, while each of these advances in ureteral reconstruction were made easier with the aid of robotic technology it was acknowledged that a true clinical outcomes advantage relative to traditional open techniques has yet to be shown.

Dr. Brian J. Flynn, a reconstructive urologist from the University of Colorado, and Dr. Benjamin Breyer, a reconstructive urologist from the University of California San Francisco, discussed their experience with acquired bladder neck pathology. Traditionally, bladder neck contractures after benign prostatic hyperplasia (BPH) surgery and vesicourethral anastomotic stenosis (VUAS) after radical prostatectomy (RP) were managed first with endoscopic techniques (eg dilation, incision ± injection with antifibrotic agent) and thereafter with failures using open, perineal exposure techniques, the latter leading to a near 100% chance of postrepair incontinence. Therefore, both discussed that the major advantage to the robotic repairs is their ability to stay proximal to the external sphincter. For contracture after BPH surgery they recommended robotic repair using V-Y or T-plasty (a) and free-graft buccal mucosa (BMG) inlayed into a subtrigonal incision (b).

**Figure 1. Robotic buccal onlay ureteroplasties.**

**Figure 2. Robotic repair using V-Y or T-plasty (a) and free-graft buccal mucosa (BMG) inlayed into a subtrigonal incision (b).**

**References**

Crossfire: Robotic Reconstruction ▼ Continued from page 35

subtrigonal incision (fig. 2).

For VUAS after RP they recommended robotic excision and primary anastomosis (VUAS primary repair). In some circumstances (such as in radiated fields) buccal graft augmentation may not be feasible, and chronic suprapubic tube catheterization or urinary diversion might be best for that patient’s quality of life.1,3-5 Both acknowledged that while the near universal use of robotic assistance for prostatectomy has decreased the overall rate of VUAS, when they do develop postoperatively the same technology that caused them is likely best suited to fix them. Similarly, although less time was devoted to urinary fistulas given their relative rarity, adequate exposure and visualization is often the major challenge to repair, and similar concerns with postfistula repair incontinence exist with repairs of urinary-rectal fistulas. A suprasphincteric robotic approach has been described by many but with such rarity that success rates are difficult to compare with open techniques, although similar to all innovative techniques, if the surgeon believes the new procedure is best for the disease process and the patient its use should be explored and perfected.

In summary, the same advantages offered to oncologists—namely visualization, access, decreased blood loss and improved convalescence—by robotic technology are being embraced by reconstructive urologists. Whether or not robotic repairs can or should replace traditional repairs is unknown, but these questions will undoubtedly continue to be asked with increasing frequency as the technologies continue to improve and the reconstructive urologist’s familiarity with the technology increases. ◆

The Urological Impact of COVID-19: Wave 2

With the impact of the COVID-19 pandemic continuing to be felt around the world, its effect on the specialty of urology has also been significant. As a way to better assess its true impact on urology, the AUA conducted a global online member survey in April (Wave 1) of this year. Results from this survey covered the personal and practice impacts of the pandemic on AUA members. In order to see how these findings have changed since April, a second survey (Wave 2) was sent to AUA members in September. A total of 3,102 members completed the 2 surveys (2,052 in Wave 1 and 1,050 in Wave 2), including 1,942 from the United States and 1,160 international members. Throughout the surveys, responses were captured from 100 countries and all 50 states.

The Wave 2 survey results revealed the impact of COVID-19 on the clinical practice of AUA members continues to be significant. Only a quarter of AUA members indicated their practice is back to 100% normal (ie pre-COVID-19 levels). Additionally, members continue to indicate the COVID-19 pandemic has had a significant financial impact on their practices. More than a third (35%) indicated their practices or institutions have reduced urological staff (down from 54% in Wave 1) and a similar amount (34%) are receiving reduced compensation (down from 40% in Wave 1), while 9% are still not currently receiving a pay check (down from 14% in Wave 1). Significantly fewer AUA members continue to indicate they have been laid off (4% each Wave), have filed for unemployment (3% each wave), plan to retire (3% each wave) or work in a practice that is planning to close (3% each wave) because of the COVID-19 pandemic (fig. 1).

The personal impact of COVID-19 on AUA members continues to be significant as well (fig. 2). Three-quarters of AUA members continue to report increased stress levels due to COVID-19 (78% in Wave 2 vs 75% in Wave 1). Nearly three-fifths (58%) in Wave 2 vs 64% in Wave 1) of AUA members are worried about becoming infected with COVID-19 while working, and more than three-quarters think their mental health and that of their colleagues has been challenged during the COVID-19 pandemic (77% in Wave 2 vs 76% in Wave 1).

Figure 1. Financial impact of COVID-19.

Figure 2. Personal impact of COVID-19.
Background
The retrocaval ureter (RCU), also known as the circumcaval ureter or preureteral vena cava, is a congenital anomaly characterized by the posterior location of the right ureter with respect to the vena cava, causing extrinsic compression associated with hydronephrosis and potential renal dysfunction, first described by Hochstotter in 1893. The classic treatment was described as the excision of the retrocaval segment, anteposition and ureteroureteral or ureteropelvic anastomosis. This reconstructive operation was generally performed with an open approach and although effective was invasive and associated with the morbidity of an open approach.

The development of minimally invasive surgical technology and techniques has been the treatment of choice for the repair of RCU in recent years. The first laparoscopic reconstruction of RCU was reported by Baba in 1994, and Gundeti began the robot-assisted laparoscopic correction of RCU in 2006. This reconstructive operation was generally performed with an open approach and although effective was invasive and associated with the morbidity of an open approach.

The development of minimally invasive surgical technology and techniques has been the treatment of choice for the repair of RCU in recent years. The first laparoscopic reconstruction of RCU was reported by Baba in 1994, and Gundeti began the robot-assisted laparoscopic correction of RCU in 2006.

Case Presentation
A 29-year-old female with a 3-year history of right flank pain associated with fluid intake also had an associated history of recurrent urinary tract infections. Physical examination revealed tenderness in the right costovertebral angle.

Ultrasound showed right hydronephrosis, and a computerized tomography (CT) urogram revealed ureterohydronephrosis with the “fishhook” sign and a posterior situation of the ureter related to the inferior vena cava (IVC; fig. 1), establishing the diagnosis of RCU.

A robot-assisted laparoscopic repair was performed with the da Vinci® Si system using 3 arms and an assistant port. The approach was transperitoneal retrocolic, identifying the ureter and carefully dissecting it from the lateral border of the IVC (fig. 2, A). The ureter was transected with resection of the atretic segment, anterior transposition and spatulation of the proximal and distal segments (fig. 2, B). A tension-free, end-to-end ureteroureteral anastomosis was performed with 3-zero absorbable monofilament suture, first placing interrupted stitches at the apex of the spatulation in the ureteral segments to properly align the repair and then in a continuous running way at the anterior and posterior aspects of the anastomosis (fig. 2, C and D). A 6Fr 22-cm Double-J® stent was placed in a retrograde fashion under laparoscopic vision, and a penrose drain was laid. The operative time was 110 minutes with blood loss of 50 ml. The hospital stay was 2 days with removal of the urinary catheter at 24 hours, drainage at 48 hours and Double-J catheter 6 weeks later. Followup was performed with urine culture at 10 days, renal urography at 6 months and diuretic renal scan 1 year later (fig. 3).

Discussion
RCU is a congenital condition characterized by the persistence of the posterior subcardinal vein on the right, which causes the proximal ureter to deviate medially and posteriorly to the IVC before resuming its natural course anteriorly and laterally. RCU has an estimated prevalence of 0.13% and is more common in men at a ratio of 3:1. Usually it becomes clinically apparent in the third or fourth decades of life, but many cases are clinically silent and could be diagnosed incidentally with the finding of hydronephrosis during imaging investigations. We report the case of a female in her third decade with symptoms of obstruction and secondary urinary tract infections.

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When projecting the impact of the COVID-19 pandemic, member outlook continues to be cautious. The number of AUA members who agree that the COVID-19 crisis will be under control in their area in the next 3 months has actually decreased since Wave 1 (38% in Wave 1 to 25% in Wave 2), and fewer than a third (29%) agree they will be back to normal clinical practice 6 months from now (compared to 45% in Wave 1, fig. 3). The outlook on attending in-person medical conferences continues to be reserved with only 28% agreeing they will be able to physically attend medical conferences by May of 2021. Members project an increase in telemedicine with nearly three-fourths (73%) in Wave 2 agreeing they will use more telemedicine in the future because of COVID-19.

Finally, new to Wave 2 were questions concerning the affect COVID-19 has had on urological health care. Results show that the pandemic has had a significant effect in this area as nearly all AUA members (92%) have seen patients because of this delay in urological care. Additionally, because of this delay in urological care more than two-fifths (42%) of AUA members have seen an increase in acute cases.

With the ever-changing dynamics of the COVID-19 pandemic the AUA believes it is important to continually monitor the effect it is having on our members. Data gleaned from these surveys will be used to determine how the AUA can best provide resources to our members and help them during this difficult time. To that end, we plan to redeploy this survey in 2021 to understand how results are changing over time and to ensure we are continuing to support our members and the global urological community.

Case Report

When present, the symptoms usually include abdominal pain, hematuria, infection and urolithiasis. Renal pain/colic appear in most identified cases (70.7%), followed by urinary infection (23.5%) and hematuria (21.6%).

RCUs have been classified into 2 types. Type I, the more common form, is a low loop of the proximal ureter. It shows a typical obstruction at the edge of the iliopsoas muscle, at which point the ureter deviates cephalad before passing behind the vena cava. It leads a proximal ureteral dilation and hydronephrosis, demonstrating a “fishhook” sign like in our patient (fig. 1). Type II, the rarer form, is a high loop of the ureteropelvic junction.

Seo et al described several factors that affect the technical aspects of laparoscopic reconstruction including a retroperitoneal vs transperitoneal approach. We utilized a transperitoneal retrocolic approach as it provides a large operative field with an excellent view.

A second factor is whether or not to excise the obstructed ureteral segment. We excised the atretic retrocaval segment of the ureter and made a precise spatulation helped by the 3D vision and “wrist” technology of the robotic platform.

An additional factor is whether to insert a Double-J ureteral stent and how to insert it. We decided to insert a Double-J ureteral stent in a retrograde fashion as we believe it is easier and faster.

A final factor is the anastomosis method. This procedure is the technically challenging part because it is the most difficult and time consuming. However, the advantage of robotics is its ability to facilitate intracorporeal suturing in an efficient manner.

Temiz and colleagues compared 2 different cohorts of RCU repair, one laparoscopic and the second with a robotic approach, describing that the mean operative time was significantly shorter (92±48.27 vs 190±46.36 minutes) with the robotic approach without any complications. In our case the operative time was 110 minutes.

Conclusion

RCU is a rare condition that should be approached with minimally invasive surgery. Robotic surgery features offer advantages over pure laparoscopy, simplifying and shortening a technically demanding procedure.
An Update on the 2021 AUA Annual Meeting

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There is no higher priority to the AUA than the health, safety and well-being of our members and the urology community. As mentioned in our September announcement, given the persistent surges of COVID-19 and unknowns relative to the pandemic, the 2021 AUA Annual Meeting will now be held in-person Friday, September 10 through Monday, September 13, 2021 in Las Vegas, Nevada at the Sands Expo Convention Center.

As part of this decision the AUA Board of Directors conducted significant assessments and scenario planning efforts focused on the safety and well-being of our many members, staff and guests at the annual meeting. Travel restrictions, possible new outbreaks of COVID-19, the availability of speakers, as well as the nature of the educational, research and networking activities were all considered as part of this careful decision.

Due to this shift many annual meeting related deadlines such as registration and abstract submission have also been extended. The abstract submission deadline has been extended to March 1, 2021 to ensure the most up-to-date science is presented at AUA2021. Registration for the annual meeting will also shift, and we anticipate opening registration within the first quarter of 2021.

We are looking forward to being back together in person as a urology community in Las Vegas next fall. The AUA is working with our partners to ensure a number of safety precautions will be in place for our in-person meeting, including widespread availability of hand sanitizer, special attention to food and beverage, and increased spacing in the meeting sessions. We are grateful for the well-received feedback from the urology community on the rescheduling of our meeting.

While we hope you will join us in person the AUA is exploring virtual options for the annual meeting including making a limited number of sessions available online via a mix of livestream and recorded webcasts.

The AUA Board of Directors and I sincerely appreciate your patience and understanding during these challenging times. We are grateful for the support of our members and urology community.

We look forward to seeing you in Las Vegas next September!

For additional information on the AUA Annual Meeting visit www.AUA2021.org.

Looking Back on 2020

Michael T. Sheppard, CPA, CAE
Linthicum, Maryland

When I sat down to write this column 1 year ago, the AUA was preparing for 2020, building a robust schedule for the year. The Annual Urology Advocacy Summit was a few short months away and AUA20 was on the horizon. Indeed, we had a grand plan that we could not wait to share with our members around the globe. But let’s face it—2020 was not the year any of us hoped it would be. Instead, it was a year of resilience, a time when our crisis plans were put to the test and a season for innovation on many levels.

Across the world, AUA members showed spirit, innovation and commitment in the face of the pandemic, and I am proud to be the CEO of this organization and a member of the global urology community. 2020 has been the year for us to truly appreciate the technology that has brought us all together and allowed us to move forward in spite of the pandemic that has turned the world on its head. Two main takeaways from 2020 are the more widespread adoption of telemedicine and expanded virtual meetings and programs.

The Rise of Telemedicine

The AUA has been a supporter of telemedicine for many years, feeling strongly that this mode of health care delivery has a number of benefits including access to care for patients in rural areas without ready access to a provider. When the pandemic closed medical offices, paused elective surgeries and minimized health care access for everyone—regardless of where they live—telemedicine emerged as a viable way to ensure that patients received much needed continuity of care from the safety of their own homes.

AUA members rose to meet this challenge, and in 2020 our community saw significant growth in the use of telemedicine. When we first surveyed our members in April regarding the impact of COVID-19 on their practices, only 29% were conducting billable telemedicine. By September that number had grown to 83%, with nearly three-quarters of respondents indicating they would be using more telemedicine in the future because of COVID-19. Payors including Medicare also saw value in telemedicine and took steps to ensure that providers received fair payment for these services to patients.

Our advocacy team along with advocates from other medical specialties worked diligently with lawmakers and regulators to demonstrate the value that telemedical services bring to the provider–patient relationship and have been actively engaged in work to maintain the provisions put in place during the public health emergency. As I write this column we await final guidance from the Centers for Medicare & Medicaid Services about the extent to which these services will be reimbursed in 2021.

Virtual Programming and Meetings

The AUA is a member organization, and as such among our favorite parts of the year are the activities when we see our members face to face. But even as 2020 saw meetings across the world—including our own Annual Meeting and AUA Summit among many others—move to online formats, I am proud that we were able to pivot swiftly to engage our members in this virtual way.

The AUA Virtual Experience and AUA Live brought the science and energy of the annual meeting into attendees’ homes and offices around the globe. More than 300 members registered and participated in the AUA Summit this summer, and with the help of technology we were able to deliver on our promise to bring educational opportunities and networking to our members around the world.

2020 may not have been the year any of us expected, but it was the year that pushed us forward on many levels. As we close out the year and look ahead to 2021 we celebrate this progress. On behalf of all of us at the AUA, I look forward to seeing you all in person next year!

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FROM THE  

**AUA Education Council**

**A New Self-Assessment Study Program App**

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

2020 is a year we will all remember. As health care practitioners we had to learn to practice in a new way in a new environment and with new challenges and barriers. As we have adapted to these changes we have also been exposed on a large scale to new ways of acquiring information and learning. As lifelong learners we now have almost instantaneous access to incredible amounts of information.

As education, learning and access to information have evolved the AUA has remained vigilant. And with that we are excited to announce a significant change to one of the AUA’s most popular products, the AUA Self-Assessment Study Program (SASP)! The AUA SASP is getting a major upgrade in 2021. Available in January the SASP will be offered as a mobile app. The app will not only be more convenient, but will also allow users to:

- Engage in test and practice modes
- Choose to receive all questions at once or in spaced intervals
- Sort questions by topic area and pull questions from multiple years
- Tag questions to review again, which will allow for the creation of a personalized deck.

The SASP mobile app will also include leaderboards and links to other AUA resources, including the AUA Guidelines and Core Curriculum. When you purchase the new app all of your previous years of questions will be available to you in 1 convenient location. This content will also be accessible online from a desktop as needed.

As part of this new product launch the AUA is offering new ways to purchase the SASP. New for 2021 you can purchase the app and then for a small additional fee also purchase the book. The AUA is also offering a brand new Residency Combo rate for SASP and Update Series, and a volume discount for Residency Programs.

The new SASP app will join several other AUA educational apps. If you were not aware, the following apps are available for download:

- The AUA University mobile app is a quick, easy way to access information on the go. From the app homepage, you have direct access to all AUAUniversity podcasts, the Core Curriculum and for subscribers, the Update Series Lessons and new audiobooks.
- The AUA Guidelines at a Glance
- The AUA Oral Board Study Guide
- The AUA Medical Student Curriculum

Formoreinformation on all AUA apps, go to [https://www.auanet.org/education/auauniversity/education-products-and-resources/app-store](https://www.auanet.org/education/auauniversity/education-products-and-resources/app-store).

If it has been a while since you visited AUAUniversity, your login has not changed. If you have any issues, please contact the AUA Customer Service Department at 800-908-9414 or 410-689-3917, or via [customerservice@auanet.org](mailto:customerservice@auanet.org).

If you have any ideas or suggestions for the AUA Office of Education, we welcome your feedback. Please send us an email at education@auanet.org.

FROM THE  

**Urology Care Foundation**

**Bright Lights in Challenging Times: Thank You for Joining Us**

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

This year has been full of unimaginable challenges and losses, yet throughout these demanding times we find ourselves continuing to further our creativity and demonstrate our adaptability and flexibility. The privilege of this platform allows me to share some bright news about the incredible undertakings and success stories of the Urology Care Foundation in 2020.

These accomplishments could not have been achieved without the tireless efforts of our members, volunteers, staff and Board of Directors. Our commitment to making a global impact has never been stronger. We continue to support research and educate patients, and have most recently launched 2 new global philanthropic initiatives.

**Humanitarian Award**

Announced earlier this year, our global philanthropic initiatives seek to recognize and support the many urology-specific humanitarian missions carried out around the world. The Urology Care Foundation’s Humanitarian Recognition Award aims to acknowledge an individual for outstanding demonstrated commitment to improving access to quality urological health care in underserved populations.

Our Humanitarian Grant Program will provide funding to help support the efforts of individuals and projects that provide direct urological patient care to individuals and communities in underserved areas, either within the United States or abroad.

**Strengthening Our Commitment to Research and Patient Education**

The Foundation strives to provide current and reliable urological information to the public and fund scientists on the forefront of reducing the burden of urological disease through research.

The Foundation has supported urological discovery since the initiation of its Research Scholar Award program 45 years ago. Support of our young scientists has never been more crucial than in these challenging times, especially with exciting advancements occurring at such a swift pace. I am deeply proud that our continued support of innovative research and our specialty’s young urology researchers remains steadfast as we enter 2021.

Together with the AUA, this year we recognized 21 researchers as recipients of the Urology Care Foundation Research Scholar Awards. These awards support research that drives lasting improvements in patient lives.

The Foundation continues to thrive as the world’s largest library of reliable urological patient education. These resources are developed based on AUA clinical practice guidelines and provide important information to our urology physician, patient and caregiver community throughout the world.

This year our trusted library of resources grew in excess of 400 patient education pieces. As a Foundation firmly committed to serving the patients of urology without borders, many of these resources have been translated into Arabic, Brazilian Portuguese, Hindi, Italian, Punjabi, Spanish and Urdu. We truly are on a global mission.

Additionally, earlier this year we launched a COVID-19 Resource Center to serve as a hub of urology focused coronavirus resources for patients and caregivers. It provides the latest information on telehealth, podcasts for managing urological cancer during COVID-19, frequently asked questions (FAQs) about visiting a urologist during the pandemic and much more.

UrologyHealth.org, our flagship site for all of these resources, is now generating an astonishing 1,000,000 visits per month, further putting an exclamation mark on our patient education and outreach efforts for 2020.

These meaningful accomplishments are not possible without the generous support of our community. Learn how you can support these extraordinary initiatives by visiting [www.UrologyHealth.org/Donate](http://www.UrologyHealth.org/Donate) today. Thank you!
I Took a Risk on a New Residency Program—Was It Worth It?

Rachel Engelberg, MD
New England Section Representative, AUA Residents & Fellows Committee
Worcester, Massachusetts

With growing demand for urologists we have seen a significant increase in the number of programs submitting rank lists for the AUA Match. Since 2014, 24 more programs have submitted lists, indicating a rapid introduction of new urology programs.1,2 Medical students entering the match might be reluctant to rank a new program highly because it is such an unknown. It can be an agonizing gamble. As the first resident expected to complete the full course of my program from the match through chief year, I offer a unique perspective on taking a risk on a new program.

At the start of my intern year there were 5 full-time academic faculty and 3 associated private urologists covering only a few of the major subspecialties including oncology, female pelvic medicine and voiding dysfunction, and pediatric urology. As an interviewing fourth year medical student having rotated at well-established programs, I was tentative about joining a department seemingly with so many needs left unmet. Promises were made of expanding the department, and with the fervor with which these promises were made I chose to take the Chairman and Program Director at their words.

Faculty joining a new residency program may also be skeptical about the ability of such a program to support their needs. What this attracts is fresh, young faculty with a keen interest in education and the ability to help mold a program into something formidable. As promised, my department grew at a rate faster than residents were added, ultimately providing exposure to all of the urological subspecialties. The high ratio of faculty to residents enabled us to cover a large breadth of cases regardless of training level, leading to well-rounded residents with the ability to adapt to any procedure to which we were assigned.

Over the past 4 and a half years I have witnessed and contributed to the development of a robust program with an excellent balance of clinical education and surgical training. The arrival of new faculty has brought a diversity of opinions, training cultures and residency/fellowship experiences. This has afforded us the opportunity for trial and error, resulting in at least 4 iterations of the didactic format and 3 different call schedules—so far. This I think is the greatest draw to a new program. We are able to avoid the old adage of “well, that’s just the way it is” and implement real and effective change where something is not working with input from faculty and residents alike.

The AUA Quality (AQUA) Registry: Past, Present and Future

David F. Penson, MD, MPH
Chair, AUA Science and Quality Council
Nashville, Tennessee

In October 2013 the American Urological Association’s Board of Directors made the strategic decision to develop a national, urology-specific, clinical data registry, thereby establishing the AUA Quality (AQUA) Registry. Since its inception, the real-world data collected in the AQUA Registry have been used to build a performance dashboard of quality measures at individual provider and practice levels while also driving evidence-based health services and clinical outcome research to advance the science of urology.

Performance Measures and Quality Improvement

While the initial focus of the registry was newly diagnosed prostate cancer, the AQUA Registry quickly expanded to include most major urological conditions of interest to the specialty. Today there are more than 60 process and outcome quality measures including 22 urology-specific measures to assess provider and practice performance from multiple clinical angles. Those measures encompass treatments for many major conditions encountered in urological care such as newly diagnosed prostate cancer, castration resistant prostate cancer, benign prostatic hyperplasia, urinary stones, azoospermia, bladder cancer and hypogonadism.

By monitoring and tracking measure scores and comparing them with the registry-wide benchmarks at provider and practice levels, the AQUA Registry enables urological care providers and practices to understand their performance and improve quality of care and patient outcomes. A recent study examined trends in performance scores from 4 common quality measure areas and found that early AQUA Registry participants gradually demonstrated score improvements in 3 of the 4 urological measures reviewed.1 These findings suggest that participation in the AQUA Registry contributes to enhanced quality of care. As an example, a registry participant commented that initial data showed that the practice was performing poorly on the medication reconciliation measure for the first 2 quarters of registry participation. However, after consistent use of the AQUA Registry dashboard to identify weak areas and implement process enhancements, a marked improvement was noted in measure performance.

Furthermore, as a Centers for Medicare and Medicaid Services approved qualified clinical data registry, the AQUA Registry has helped approximately 750 providers fulfill their Merit-based Incentive Payment System (MIPS) reporting each year since 2016. Additionally, the AQUA Registry can assist in professional development for registry participants through credit from the American Board of Urology’s (ABU) Life Long Learning Program. Further developmental work is underway to support registry participants with automated case log submissions to ABU, making the AQUA Registry a true one-stop-shop for facilitation of physician certification.

Data Captured in the AQUA Registry and Early Research Work

As of September 2020 the AQUA Registry includes approximately 1,700 active providers from more than 140 urological care practices, including private practices, academic medical centers and hospitals.
From the AUA Science & Quality Council

Continued from page 41

across 41 U.S. states. The AQUA Registry has captured data from more than 471 million patient visits from 7.1 million unique patients with various urological conditions.

The AQUA Registry is a valuable tool that can be used to continue the AUA’s mission to support health services and comparative effectiveness research by generating real-world evidence to guide urological practice. When using AQUA data for research purposes the first step is to identify treatment patterns and trends over time for common urological conditions. Such reviews allow researchers to build patient treatment journeys starting from initial diagnosis and continuing through various courses of treatment. Taking a recent study as an example, authors examined the management variability of urethral stricture disease (USD) in the United States using data available through the AQUA Registry. Registry data indicate that a substantial number of patients undergo repeated procedures, despite increasing evidence of the futility of repeated endoscopic management of USD while urethroplasty remains rare. It is the ultimate goal of such research to disseminate guideline based care for USD management and widen appropriate patient selection for urethroplasty. The researchers also noted a belief that the AQUA Registry has the potential to become a pivotal tool for quality reporting and enhanced decision making.

Planned Work on the Horizon

As the quality of AQUA Registry data continues to improve, further uses will be explored. AQUA data may serve as the basis for the creation of quality improvement tools, assessment and expansion of clinical guidelines, identification of areas of need in continued medical education and evaluation of existing courses, and assessment of the usefulness and relevance of quality measures from the perspectives of cost-effectiveness and patient outcomes. Moving forward, health services and outcome research using AQUA data will continue to expand to meet the needs of the urological research community.


PRACTICE Tips & Tricks

10 Reasons Why It Is Good to Be a Urologist

Neil H. Baum, MD
New Orleans, Louisiana

Every time I go to the doctor’s lounge I hear so many of my colleagues complain about their practices and express uncertainty about the future of medicine. I often hear about how they are discouraged with decreasing reimbursements, rising overhead costs and diminishing incomes. However, urologists seem to be more optimistic about and satisfied with their practices. After interviewing a few of my colleagues I decided to list 10 reasons why it is good to be a urologist.

1. Urologists are fortunate that our specialty is in growing demand. As the Baby Boomer population ages there will be more men with benign prostatic hyperplasia, prostate cancer and erectile dysfunction. There are going to be more women with incontinence and vaginal prolapse who will also need the services of urologists.

2. Although many physicians in primary care and other specialties have opted to be employed by hospitals, many urologists still continue to work in small groups where they are on track for partnership in and ownership of the practice. Just remember if you are self-employed or are working in a group practice with a road to partnership you cannot be fired or laid off in a bad economy. You have the luxury to control your work environment, which includes the number of hours you work each day, the number of patients you see and the amount of vacation time you take. The stress level goes down and the enjoyment and satisfaction from practicing medicine goes up when you are in charge of the practice, make the decisions and are your own boss.

3. It is amazing how many doctors complain about their incomes. If urologists compare the average urologist salary with those for all other jobs you will find that urologists are close to the top, preceded only by orthopedics and cardiology. The average urologist made $309,000 in 2011.1 There are many in our specialty who earn 2 or more times the average urologist.

4. In medicine there is no forced retirement. For the most part the work is not physically demanding, and urologists can work well into their 80s. According to a survey conducted by Wells Fargo 25% of respondents estimate they will need to work until at least age 80 before being able to comfortably retire.2 Many medical colleagues complain that they will not be able to retire and feel that they will need at least $2 million in savings in order to retire. The other unique feature of urology is that if urologists are not able to afford to retire they still have the option of supplementing their income by continuing to practice part time. Many physicians are choosing to work locum tenens and have the luxury of accepting a job whenever and wherever they want.

5. Many urologists enjoy the lifestyle benefits of our profession. For the most part urologists are seldom called out after hours or in the middle of the night. The few emergencies include testis torsion, acute retention with an impassable stricture and obstructed ureter with fever and elevated white count. Most urologists have normal hours and are not on call 24/7 and have a life outside of practice. For the most part urologists can work in any geographical community they choose. They can determine where they would most like to live before embarking upon their careers.

6. The practice of urology has so many unique opportunities to craft the kind of practice that we most enjoy. We can select to have a pediatric practice, geriatric practice, transplant practice, women only practice, andrology practice, minimally invasive practice or urological cancer practice. By using marketing techniques each of us can sculpt and craft the exact practice that we would like to have.

7. Most urologists enjoy job satisfaction and feel gratification from caring for our patients.

8. Urologists have a keen sense of humor. A urologist usually has a quip or joke at the ready, which is appreciated by our patients and colleagues.

9. Urologists enjoy the comradesry with their colleagues. We tend to have good relations with our fellow urologists in our communities, region and the nation.

10. Thanks to the good work of the AUA we have leadership that is focused on our needs and listening to our problems.

The bottom line is—yes—there is a lot that we can complain about. There are certain things that need to be fixed in order to rein in health care costs and still improve patient satisfaction and patient outcomes. But the dynamics within urology in the near future assure a steady increase in patients and future opportunities.

In multivariable analysis, residents were more likely to report feeling unprepared for residency if they were female (OR 1.34, 95% CI 1.15–1.57) or did not take call as a medical student (OR for 0 vs more than 4 calls, 2.72, 95% CI 2.10–3.52). Residents who did not complete a subinternship were less likely to report feeling prepared for residency (OR 0.68, 95% CI 0.48–0.96). Feeling adequately prepared for residency was associated with a nearly twofold lower risk of experiencing burnout symptoms (OR 0.57, 95% CI 0.48–0.68). In interviews, the dominant themes associated with preparedness included various regulations limiting the medical school experience, overnight call facilitating preparation and selection of a specialty compatible with their preferences, and adequate perceptions of residency improving expectations, resulting in improved preparedness, lower burnout rates and lower risk of attrition.

The authors conclude that the perception of feeling unprepared was associated with inadequate exposure to resident responsibilities while in medical school. In the era of COVID-19 we can only expect these issues to worsen.


Platinum based chemotherapy is the standard of care, first line treatment for advanced urothelial carcinoma. However, progression-free survival and overall survival are limited by chemotherapy resistance. In this phase 3 trial the authors randomly assigned patients with unresectable locally advanced or metastatic urothelial cancer who did not have disease progression with first line chemotherapy (gemcitabine plus cisplatin or carboplatin) to receive best supportive care with or without maintenance avelumab. The primary end point was overall survival. Secondary end points included progression-free survival and safety. Among all 700 patients who underwent randomization the addition of maintenance avelumab to best supportive care significantly prolonged overall survival as compared with best supportive care alone. Overall survival at 1 year was 71.3% in the avelumab group and 58.4% in the control group (median overall survival, 21.4 months vs 14.3 months, HR for death 0.69, 95% CI 0.56–0.86, p=0.001).

Avelumab also significantly prolonged overall survival in the PD-L1-positive population; overall survival at 1 year was 79.1% in the avelumab group and 60.4% in the control group (HR 0.56, 95% CI 0.40–0.79, p <0.001). The median progression-free survival was 3.7 months in the avelumab group and 2.0 months in the control group in the overall population. The incidence of adverse events from any cause was 98.0% in the avelumab group and 77.7% in the control group.

The authors conclude that maintenance avelumab plus best supportive care significantly prolonged overall survival, as compared with best supportive care alone, among patients with urothelial cancer who had disease that had not progressed with first line chemotherapy.

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