American Urological Association

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Genomic Markers—How to Choose and When to Use?

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Clinical risk groups in localized prostate cancer are determined by prostate specific antigen (PSA), clinical stage and grade (Gleason score/ISUP [International Society of Urological Pathology] Grade Group [GG]). However, substantial biological and clinical heterogeneity exists within clinical risk groups. This heterogeneity creates challenges for key clinical decisions when grouping patients into risk groups often does not allow for sufficient detail in individualizing treatment recommendations.

One approach to providing more precise risk estimates is the use of risk models such as askMUSIC and Cancer of the Prostate Risk Assessment (CAPRA). Alternatively, genomic testing can be incorporated for some patients to allow tumor biology to help inform these risk estimates.

During the last decade genomic tests have been developed and commercialized for breast, prostate and colon cancers, among others. For men with prostate cancer the 3 tissue based gene expression classifiers that can be considered currently are Prolaris®, Oncotype DX® Genomic Prostate Score (GPS) and Decipher®.

Prolaris

Prolaris is a quantitative polymerase chain reaction (qPCR) based assay that measures 31 cell cycle proliferation genes and 15 reference housekeeping genes for normalization. The assay reports a score ranging from 0 to 10, with higher scores signifying more aggressive tumors. This score is combined with standard clinical variables to report the estimated 10-year risk of disease specific mortality for a patient on active surveillance (AS) and the 10-year risk of metastasis following definitive treatment.

Oncotype DX GPS

Oncotype DX GPS is also a qPCR assay and measures the expression of 12 genes across 4 biological pathways along with 5 reference genes. The GPS report provides a score ranging from 0 to 100 and was primarily developed to estimate the risk of adverse pathology at prostatectomy, defined as Gleason 4+3 or greater, or stage pT3 or greater. Estimated risks of metastasis and death within 10 years are also provided in the report.

Decipher

Unlike the previously mentioned tests Decipher is a whole transcriptome

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Unlocking the Potential of the EHR to Advance Clinical Research

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Introduction

In the United States the adoption and integration of the electronic health record (EHR) into health care workflows are expanding the amount and type of collected clinical electronic data. While the clinical burden associated with EHR based workflows is not insignificant, EHR based data collection may reduce the financial and time burdens associated with manual data collection.[1]

Burgeoning electronic data repositories offer potential resources for clinical outcome, quality initiative and comparative effectiveness research, which are more comprehensive than administrative databases and more standardized than manual data extraction. Consequently, the

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assay (rather than qPCR) that incorporates 22 genes across multiple pathways. Scores range from 0 to 1.0, with higher values indicating worse prognosis. For untreated patients the Decipher Biopsy test reports a percentage likelihood of high grade cancer (primary Gleason 4 or 5) at prostatectomy, 5-year metastasis and 10-year disease specific mortality after radical prostatectomy (RP). For patients with higher risk disease after prostatectomy Decipher Prostate RP provides 5-year metastasis and 10-year disease specific mortality estimates.

When used appropriately these tests can aid in management decisions for the 3 distinct clinical scenarios of 1) deciding between AS or primary treatment, 2) post-prostatectomy radiotherapy (RT) and 3) identifying patients undergoing RT who would benefit from concurrent androgen deprivation therapy (ADT).

Active Surveillance vs Primary Treatment

Multiple studies, including the ProtecT trial,[1] have demonstrated the safety of AS for low risk cases. However, inclusion of some patients with favorable intermediate risk disease (NCCN® intermediate risk with GG 1-2 and less than 50% biopsy cores positive) may also be appropriate. There is a large body of retrospective data supporting the performance of each of the 3 previously mentioned tests. However, there have been few studies assessing the impact of molecular testing in clinical practice.

In a recent observational study of 3,966 patients in Michigan with newly diagnosed prostate cancer 747 (18.8%) were determined to have undergone testing with the Oncotype DX, Prolaris or Decipher platforms.[2] Of 1,487 favorable risk cases 320 (22%) had testing, and 76% of those with a test result below the proposed assay specific thresholds were managed on surveillance. In comparison, 46% with an above threshold test result were managed on AS and 58% of those not tested went on surveillance. Molecular testing with a result below threshold was independently associated with AS, indicating that testing appears to influence management of newly diagnosed cancer.

It is important to note that not all men with low or favorable intermediate risk cancer need these tests. The G-MAJOR (Genomics in Michigan to AdJust Outcomes in prostate canceR) study, set to open in early 2020, will prospectively randomize favorable risk patients to testing vs no testing and will help determine which men are likely to benefit from molecular diagnostic testing (fig. 1).

Use of Postoperative Radiation

While the debate between adjuvant and early salvage RT has been renewed with the recent release of early results from key randomized controlled trials such as RADICALS, there remains a critical need for postoperative radiation (adjuvant or salvage) in appropriately selected patients.

Prolaris and Decipher have been studied in the post-prostatectomy setting. For Decipher retrospective data indicate that patients with high scores may benefit from early postoperative RT while those with low scores do not benefit from early RT.[3] As in the newly diagnosed patient setting the clinical utility of genomics in this space remains to be determined.

One published study indicates that Decipher testing may impact treatment decisions and decrease cancer related anxiety.[4] The G-MINOR (Genomics in Michigan ImpactiNg Observation or Radiation) trial, which randomized patients after prostatectomy to a Decipher arm and a control arm, will provide additional insight into the clinical utility of genomic testing in this setting (NCT02783950) (fig. 2). Accrual was completed in 2018 and initial results are anticipated in 2020.

Androgen Deprivation Therapy with Radiation

Multiple studies have demonstrated that ADT improves overall survival for intermediate and high risk patients undergoing RT. These data rely on conventional risk stratification based on clinical variables such as T stage and PSA and, therefore, allow for potential disease heterogeneity within risk groups. In particular, among intermediate risk patients, those with unfavorable intermediate risk disease receive the most benefit from ADT. Genomic testing may offer an approach to more accurately identify this subgroup of patients who need ADT.

In a post hoc analysis of a prospective cohort of men with unfavorable intermediate risk disease treated with RT alone, those with low Decipher scores had no metastatic events at

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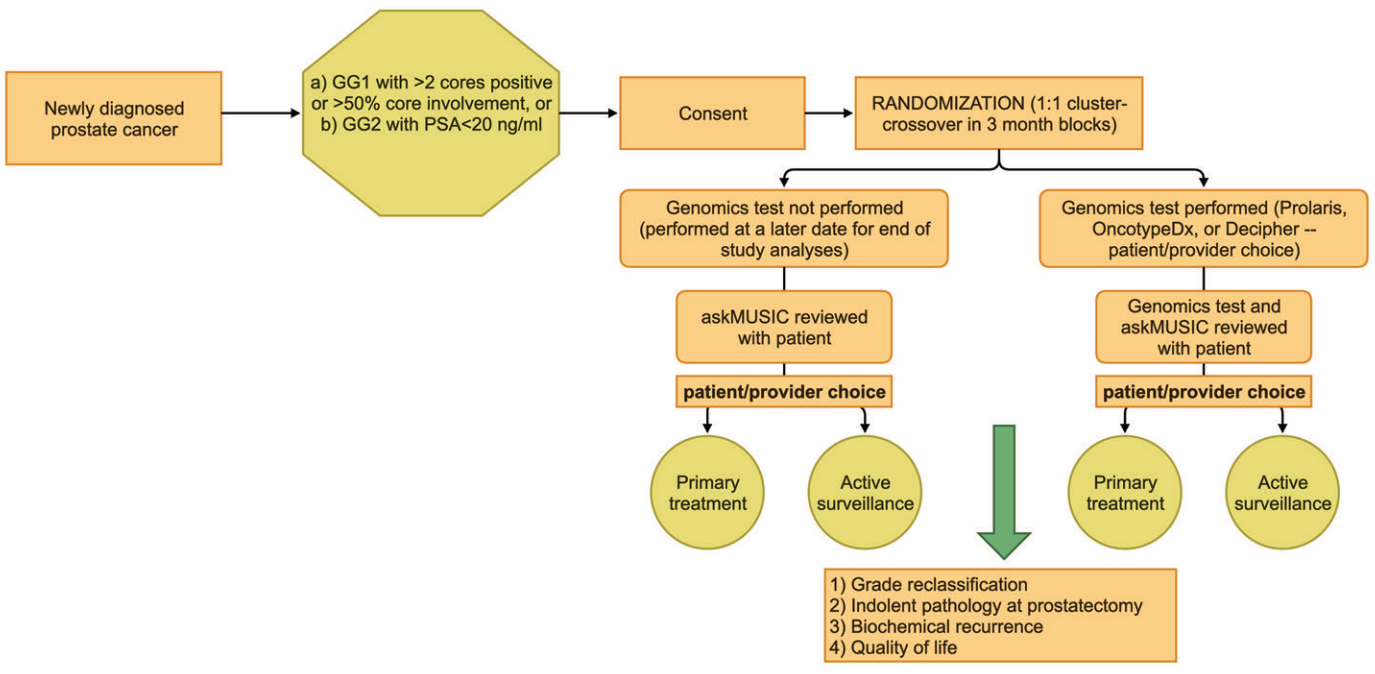

Figure 1. Overview of G-MAJOR randomized controlled trial.

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Use of Genomic Markers

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10 years following treatment.[5] More work is needed to understand how genomic testing can guide intensity of treatment.

Conclusion

Currently no comparative data exist for the 3 tests and choosing among them is likely less important than understanding when to use these assays. Use of reflex testing, ie automatic ordering after a prostate biopsy returns positive, is inappropriate. Like all laboratory tests these assays should only be used when a clinical decision might be impacted.

For very low risk cases there is little indication that genomic testing has a role in decision making as there is a preponderance of data to support the safety of AS regardless of any gene expression classifier results. There is a clear need for prospective randomized controlled trial data, and data from G-MINOR and G-MAJOR should help address this need. ◆

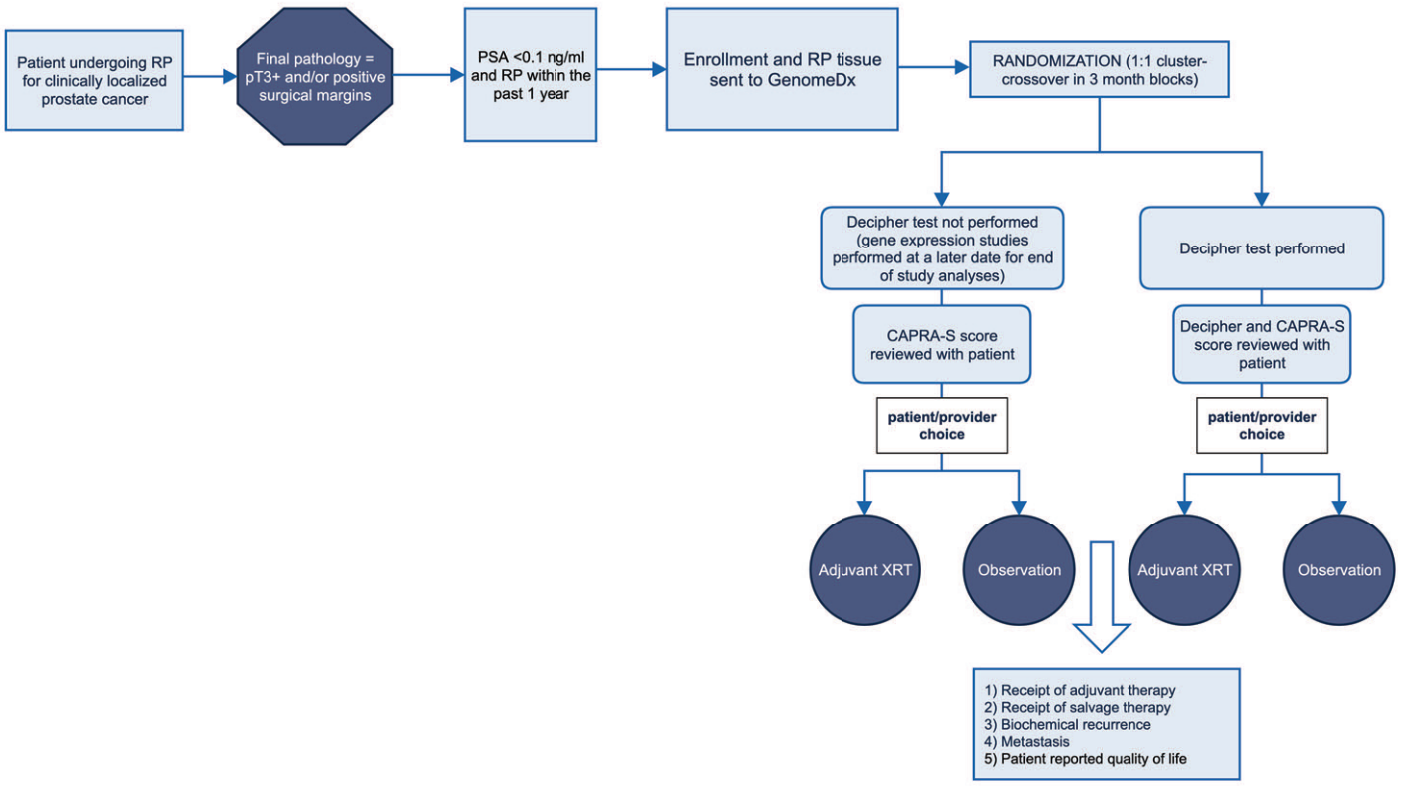

Figure 2. Overview of G-MINOR randomized controlled trial. *XRT*, radiation.

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Use of EHR to Advance Clinical Research

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EHR provides a valuable resource for clinical research when the benefits and limitations are understood.[1]

Planning is critical and must include an assessment of research goals, existing resources, and feasibility of alternate approaches to supplement data gathering. We compare existing EHR based tools for research and share lessons learned after incorporating EHR data collection into routine pediatric urological practice (see Appendix).

Enhanced Lists

Creating an enriched list of patients from the EHR using criteria such as age, ICD-9/ICD-10 codes and encounter dates, and then augmenting with chart review of narrative text in clinical notes, discharge summaries and operative reports, is the most straightforward approach to EHR based data collection. Advantages of this method include relative ease of data extraction, increased patient identification, and efficiency and scalability across sites.

The main drawback is that this approach still necessitates manual chart review and, in the absence of standardized charting, important details such as operative nuances may not be captured by nonclinical research personnel. Therefore, enhanced patient lists alone are not a sufficient foundation for EHR based research.

Electronic Data Extraction Using Preexisting Data Fields

This method involves extracting data from preexisting, standardized EHR data fields embedded in clinical workflows such as demographics, orders, machine generated laboratory results, flowsheets, vital signs, appointment schedules and billing data.[1] Data are standardized a priori, which not only facilitates data extraction but also allows for homogenous data collection across multiple specialties within an institution and across multiple institutions.[2]

Limitations include the need for sophisticated, comprehensive data extraction programs to ensure data are captured across workflows and gathered from multiple sources (eg physician visit, outpatient clinic, emergency department), and that no one type of patient encounter will capture all patients with a certain diagnosis.[3] Data variability issues can be exacerbated in multicenter research when participating institutions have different storage structures, requiring system specific extractions and data management.

Regulatory and institutional limitations to data sharing may prohibit the extraction of certain data to ensure privacy, thereby further limiting data available for the pooled analysis.[4] Well tailored research questions, data quality review to ensure accuracy and augmentation of preexisting field data capture with multiple data sources facilitate needed completeness for research analysis.

Structured (Discrete) Data Entry

All EHR systems permit creation of structured data entry systems, which are user designed and developer created electronic forms or templates created to optimize data completeness and standardization.[5] Check boxes or drop-down menus are used to capture a wide variety of data, including patient complaints, imaging findings or treatment plans. These templates can be modified to match encounter specific variables and insert data in existing structured reports so anyone reviewing the notes can see the information in a structured narrative format.

Integration of unstructured text with discrete data fields facilitates physician data capture, allows freedom of expression, supports sharing of standardized data among EHR systems, and provides structured data for meaningful use reporting, quality assurance and clinical research.[1] The significant up-front cost and time to create data collection/clinical documentation, provider cooperation to implement similar clinical documentation approaches and the potential impact of additional required data elements on clinician workflow are all limitations.

Natural Language Processing

Natural language processing (NLP) uses computer algorithms to identify

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and extract structured data elements from the unstructured text (often called free text) that makes up much of existing clinical documentation. Ideally NLP can convert provider narratives into discrete variables, which can then be stored in structured databases for analysis.[1] For example, information extraction, a common NLP method, allows data extraction and continued unlimited clinical expressiveness without impacting existing clinical workflows.

While the up-front costs of NLP are minimal, the resources needed to produce an analysis ready database can be extensive. Available text often contains nonstandard abbreviations and variant spellings of similar words, resulting in wide variation and challenging NLP effectiveness. To mitigate limitations data may be "pre-processed" by using spell checking, word sense disambiguation to identify the correct meaning of words with multiple meanings, and marking words as a particular part of speech (nouns vs verbs vs adjectives).[1] Because NLP programs are attuned to detect specific provider or department idiosyncrasies, they are not generalizable to other research applications or easily scalable across practice settings.

Conclusions

While the EHR offers significant potential to facilitate clinical research, the relative benefit of this resource must be weighed against potential up-front costs and impact on clinical workflow. As discussed, there are several approaches to using the EHR to facilitate research, each with strengths and weaknesses. In our practice multiple approaches, such as use of preexisting data fields in conjunction with structured data elements or limited manual chart review, allow for robust data capture needed to answer research questions while minimizing the impact on clinical workflow.

Planning is critical to determine what approaches are available and feasible based on research goals, resources and experience. When using the EHR to facilitate multisite research it is even more essential to ensure a common understanding of research concepts, to optimize surgeon buy-in to alterations to workflow, and to use quality checks to ensure data compatibility before wide scale implementation to facilitate effective collaboration and minimize the risk of unanticipated issues once data collection has begun.

Despite these limitations we believe that the EHR offers a promising alternative to traditional research methods and may help expand the reach of research participation by overcoming the hurdles of time and human resources associated with traditional research. ◆

Appendix. EHR based data use methodologies

	Enhanced Lists	Direct Extraction from Preexisting Fields	Structured Data Elements	Unstructured Data Extraction (Natural Language Processing)
Approach:	• Use ICD-9/10 codes, date ranges, or other standardized data to (1) generate a potential patient cohort, (2) extract data from identified fields, and (3) abstract other relevant data using traditional chart review or other EHR data extraction methods	• Data extraction from preexisting standard, embedded data field, such as demographics, orders, machine-generated lab results, vital signs, appointments, and billing data	• Development of customized structured data elements embedded in EHR to allow for capture of specialty-specific data metrics	• Use of specialized computer algorithms to convert unstructured text into structured data elements
Strengths:	• Increases eligible patient identification efficiency. • Permits more flexibility in data extraction by coupling with traditional chart review than allowed by extraction from structured data elements • Less upfront cost due to lack of need of specialized data element development or data extraction algorithms	• Allows for data extraction using standardized reporting tools. • Flexibility of use across multiple clinic workflows • Little cost due to lack of need of specialized data element development or data extraction algorithms • May facilitate multicenter research due to lack of need for development of customized structured data elements	• Allows for comprehensive data capture tailored to specific research questions	• Minimal impact on clinical workflow; allows for variations in clinical documentation
Weaknesses:	• Requires additional resources such as trained chart reviewers, structured data elements, or natural language processing for data extraction	• Limited scope of data available. Variations in data capture from different workflows or different sites. • Limited ability to obtain data from incomplete encounters or outside records. • Limited ability to identify temporal relationships.	• Upfront cost of development of customized data elements and extraction. • Impact on existing clinical workflow due to changes in clinical documentation. • Potential difficulty of expansion across multiple centers due to differences in EHR support and expertise.	• Significant cost and expertise needed to extract meaningful data due to variations in text • May not capture text due to uncommon abbreviations or documentation "cut and paste" • Impacted by minor changes in documentation • Limited ability to identify temporal relationships • May not easily be expanded to other centers

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If Not Cytology, What if Any Biomarker Should I Use?

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Bladder cancer has a high risk of recurrence and progression. As a consequence, patients undergo close surveillance to facilitate early detection of disease recurrence.[1] Most patients undergo white light cystoscopy but there is concern that some papillary disease and in particular carcinoma in situ (CIS) can be missed. Enhanced cystoscopy such as blue light fluorescent cystoscopy and narrow band imaging have demonstrated improved detection of bladder cancer but their use and availability for surveillance in the urology clinic are still limited.

Cytology is a noninvasive test that has been used for decades as an adjunct to cystoscopy, with the goal to help identify cancer missed by cystoscopy. The utility of cytology has come into question with some recent studies finding that the sensitivity for low grade disease is very poor (less than 30%), and that even the sensitivity for high grade disease is lower than desirable (50% to 80%).

A systematic review of the literature found 29 relevant studies with 12,566 patients with a median sensitivity for voided cytology for lower risk tumors (pTa, G1, G2), higher risk tumors (pT1, G3, CIS) and CIS alone of 27%, 69% and 78%, respectively.[2] A more recent analysis of 1,487 urine samples from 1,375 patients demonstrated a pooled sensitivity and specificity for cytology of 40.8% and 92.8%, respectively.[3] The pooled sensitivity was 11.4% for low grade/WHO grade 1 disease and 54.3% for high grade/WHO grade 3 disease.

Additionally, cytology is a subjective test with significant interobserver variability.[4] The question at hand is whether cytology still serves the needs of the urologist and patient with bladder cancer and if not, are there better alternatives?

Multiple urine based tumor markers have been developed to identify abnormalities in the urine associated with cancer due to changes in proteins, cells, DNA, RNA, methylation or other cellular components. Most urine markers have an improved sensitivity for low grade cancers but overlapping sensitivity for high grade disease and CIS.

The main limitation for current urine markers is a lower specificity compared to cytology, which results in a larger percentage of false-positive results. There is also a paucity of prospective studies evaluating clinical utility. As such, the role for markers needs to focus on areas in which cytology underperforms or urine markers may have unique advantages.

The most established role for urine markers is in the setting where cytology has already been used and resulted in atypical findings or in patients with equivocal cystoscopic findings and negative or atypical cytology.[1] The 2 markers with potential utility in this setting are UroVysion FISH assay and Cxbladder Monitor.[5,6] In this setting patients with an abnormal marker are at considerably higher risk for cancer and these patients should have close surveillance, enhanced cystoscopy or biopsy to further evaluate the bladder. Also, consideration should be made for upper tract imaging if not recently performed.

For other clinical scenarios there is still a potential role for markers but less evidence to support their use at this time. For example, replacing cystoscopy is a potential option since many markers report very high negative predictive values. The problem is that negative predictive value, unlike sensitivity, is inversely correlated with disease prevalence. Therefore, a high negative predictive value is to be expected when even a marginally sensitive marker is used in a low prevalence setting such as cases of microhematuria.

Whether such a method is safe and acceptable to patients has not yet been established. For patients with high risk disease the risk of progression and concerns about a false-negative marker result may exceed the willingness to avoid cystoscopy. However, for patients with low grade, intermediate risk disease a urine marker may be considered in a role alternating with cystoscopy. Such a strategy could be cost-effective but a prospective study would be necessary to demonstrate safety.[7]

In terms of replacing cytology the pertinent issue is demonstrating that a positive marker is "actionable." The current recommendation for patients with a positive cytology is biopsy of the bladder and upper tract imaging due to the high positive predictive value of cytology. The data are insufficient to evaluate the true positive predictive value of urine markers in the setting of a normal cystoscopy and positive marker. Studies would need to be performed in patients with a normal cystoscopy and positive marker in which all those with a positive marker underwent biopsy. This type of study would then validate the value of using a marker to detect cancers missed by cystoscopy.

The rapid proliferation and dropping costs of "-omic" technologies will likely lead to further development of novel bladder cancer markers. After establishing diagnostic accuracy, the challenge for researchers will be to show clinical utility and cost-effectiveness before the adoption of markers becomes widespread. ◆

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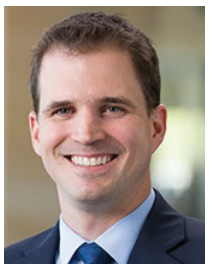
Do We Monitor Too Much for Low Grade Bladder Cancer?



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Nonmuscle invasive bladder cancer represents about 70% of newly diagnosed bladder cancer. Risk stratification by grade and stage assists urologists in determining the most appropriate treatment recommendation and surveillance strategy.[1] Surveillance of low grade disease usually consists of office cystoscopy and cytology in appropriate risk patients. Some studies have reported that urologists overuse cystoscopy in this population, which may have cost and quality implications.[2]

Low grade Ta urothelial cell carcinoma (UCC) of the bladder can be categorized into low or intermediate risk depending on focality, size and presence of invasion. In low risk cases the AUA guidelines recommend performing the first surveillance cystoscopy within 3 to 4 months followed by surveillance cystoscopy 6 to 9 months later and annually thereafter. Additionally, in asymptomatic patients routine upper tract imaging is unnecessary due to the low incidence of subsequent upper tract disease.

Conversely, more aggressive surveillance is recommended for patients with low grade disease and intermediate risk of recurrence (multifocal, large volume or superficially invasive). Cystoscopy and urine cytology are performed every 3 to 6 months for 2 years, every 6 to 12 months for years 3 and 4, and annually thereafter. In contrast to the low risk cases, cross-sectional imaging should be considered in this population, although data are limited on the use of cross sectional imaging in some subsets.

Similarly, evidence to support one surveillance schedule over another in patients with low grade noninvasive UCC is sparse. Olsen and Genster compared outcomes of patients assigned to different surveillance regimens in a randomized controlled manner.[3] The surveillance regimens included follow up 1) every 3 months for the first 2 years, every 6 six months in year 3 and annually thereafter or 2) every 6 months for the first year and once per year thereafter. There was no difference in regard to recurrence, progression or death between the groups. The study was limited in that the population was small (97), and cystoscopy was performed annually in both cohorts with other follow up appointments consisting of abdominal ultrasound to evaluate the bladder.[3]

Some studies have evaluated the natural history of low grade Ta UCC and, although recurrences are not uncommon and can be managed in systematic fashion with in-office biopsy/fulguration or operative excision, progression may be a cause for concern and hesitation to prolong surveillance. Recurrence rates for low grade Ta UCC can be high, with some studies reporting overall rates as high as 50%.[4–9] Most recurrences are low grade in nature and can be associated with increased tumor focality, size and lack of perioperative intravesical chemotherapy.[9,10]

The evidence pertaining to progression after diagnosis of low grade Ta disease has been evaluated in several retrospective studies with similar results, as overall progression (stage/grade) rates in patients with long follow up (ie greater than 5 years) have ranged between 10% and 20%.[5] Tumor progression to muscle invasive bladder cancer has occurred in approximately 2% of patients.[4,6,8] Predictors of progression have consistently included tumor multifocality while tumor size has been identified as a factor in some studies.[6,8,11]

Timing can also be important when considering risk stratification, treatment and surveillance for low grade Ta UCC of the bladder. For instance, some studies have found that tumor status early in surveillance was a strong prognostic factor for recurrence, and patients who are disease free for 5 years have a greater than 98% chance of being disease-free in the long term (ie 20 years of follow-up).[12] Progression is also usually time dependent as progression occurs in the majority of cases within the first year of diagnosis and nearly all occur within 5 years of diagnosis.[4,9,12] However, there are some large series that have reported progression of disease after 5 years, and approximately 2% of patients will ultimately die of disease.[8,10,12]

Health care cost implications are also important to consider when discussing surveillance frequency. Linton et al evaluated the efficiency of surveillance cystoscopy in patients with low grade Ta UCC of the bladder and found that to detect a single recurrence, grade progression or muscle invasion progression, approximately 7, 147 and 675 cystoscopies would have to be performed,

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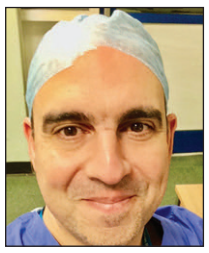
CASE *Report*

Solitary Bone Metastases—Where do They Come From?



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Clinical Case

A 68-year-old woman was seen in the orthopaedics outpatient clinic complaining of gradually worsening diffuse pain around her right shoulder and upper arm following a low energy trauma during daily activities. Medical history was only significant for knee osteoarthritis and asthma. She was a chronic smoker and was taking simple analgesics regularly. Clinical examination was restricted by diffuse tenderness around the right shoulder and upper arm.

X-ray of the shoulder demonstrated a fracture through the base of the coracoid process as well as the proximal humerus (fig. 1). Magnetic resonance imaging of the right shoulder showed pathological fracture to the proximal humeral metaphysis caused by a likely metastatic 5.5 cm infiltrative lytic lesion (fig. 2). Whole body nuclear scan confirmed the fracture but refuted widespread bone metastases (fig. 3). Further scans were performed to identify the primary

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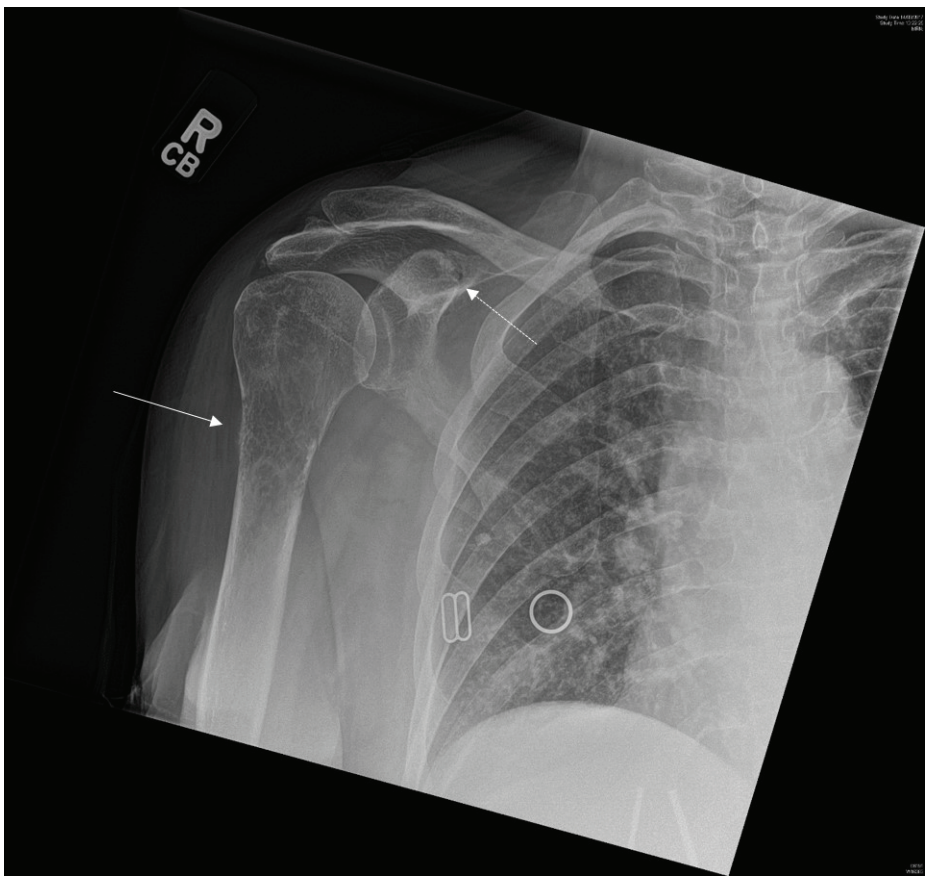

Figure 1. X-ray of right shoulder reveals fracture through base of coracoid process (dotted arrow) and proximal humerus (arrow) at level of surgical neck secondary to lytic lesion, most possibly metastatic in origin.

Monitoring Low Grade Bladder Cancer

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respectively. [13]

Given the self-evident financial stress this places on patients and payers,[14] some are now considering active surveillance for the appropriately selected patient with low grade noninvasive appearing bladder tumors. The best candidates for this approach tend to be patients with medically comorbid conditions and solitary small papillary bladder tumors that otherwise cannot be safely managed in the clinic. Ideally, these patients have negative cytology, no symptoms and no history of carcinoma in situ or high grade disease.

In several small studies on outcomes of active surveillance in low risk cases active surveillance failed in about 40% and required a procedure for bladder cancer within the first year due to positive cytology, symptoms (ie hematuria) and increase in number/size of tumors.[15,16] Furthermore, this approach is predicated on the notion that a urologist can accurately predict the grade and stage, something that remains very much in question.[17]

In conclusion, it is reasonable to monitor patients with low grade Ta UCC of the bladder for longer intervals in an attempt to avoid frequent procedures and office visits, reduce health care costs, and improve quality and efficiency of care. Patients with large, multifocal or superficially invasive low grade tumors are at a higher risk of recurrence and progression, and likely warrant more rigorous surveillance. Because most recurrence and progression events occur within the first year, the initial evaluation cystoscopy should be performed at 3–4 months, as the results can help guide urologists on subsequent surveillance strategies. Lastly, active surveillance of low grade noninvasive-appearing bladder tumors is gaining traction and may be a reasonable alternative for patients with low risk bladder cancer history. ◆

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FERRING PHARMACEUTICALS

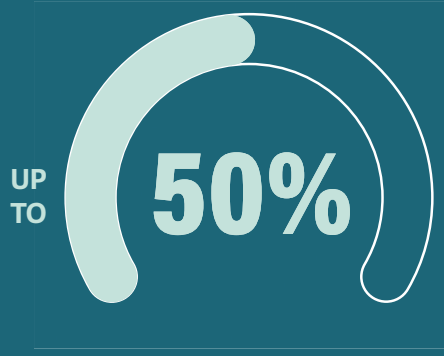
Oncology

In non-muscle invasive bladder cancer (NMIBC)

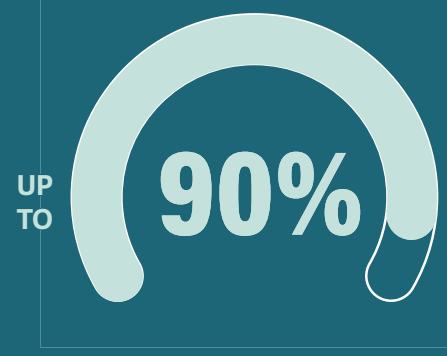
HE WISHES HE'D HAD OTHER OPTIONS. DON'T YOU?

Limited advancements in the treatment of NMIBC offer few effective options after BCG[1,2]

Recurrence is common in high-risk disease, leaving patients anxious about what the future holds, which may include radical cystectomy[1,3]*



suffer recurrence within **1 year** after intravesical therapy[4]



suffer recurrence within **5 years** after intravesical therapy[4]

ADDITIONAL SECOND-LINE OPTIONS ARE URGENTLY NEEDED

Find out why at **TheBladderMatters.com**

*A high-risk NMIBC patient is defined as a patient who presents with/exhibits any of the following tumor characteristics: high-grade T1, recurrent high-grade Ta, high-grade Ta >3 cm, multifocal high-grade Ta, carcinoma in situ, BCG therapy failure in high-grade cases, variant histology such as micropapillary and sarcomatoid, lymphovascular invasion, and/or high-grade prostatic urethral involvement.[5]

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Origin of Solitary Bone Metastases

▼ Continued from page 6

lesion. Computerized tomography (CT) of the thorax, abdomen and pelvis showed a 3.8 cm left lower pole renal lesion with appearance consistent with renal cell carcinoma (RCC) (figs. 4 and 5). There was no evidence of renal vein involvement or tumor extension beyond Gerota's fascia.

The patient underwent preoperative embolization of the lesion and right proximal humeral replacement at an orthopaedic oncology center. Histological examination of the right humeral lesion revealed features of metastatic clear cell RCC, confirmed by immunohistochemistry, positive for CD10, EMA, AE1/AE3 and CK (MNF116).

After recovery from shoulder surgery the patient was seen in the urology outpatient clinic. Following consultation she was listed for a left laparoscopic cytoreductive

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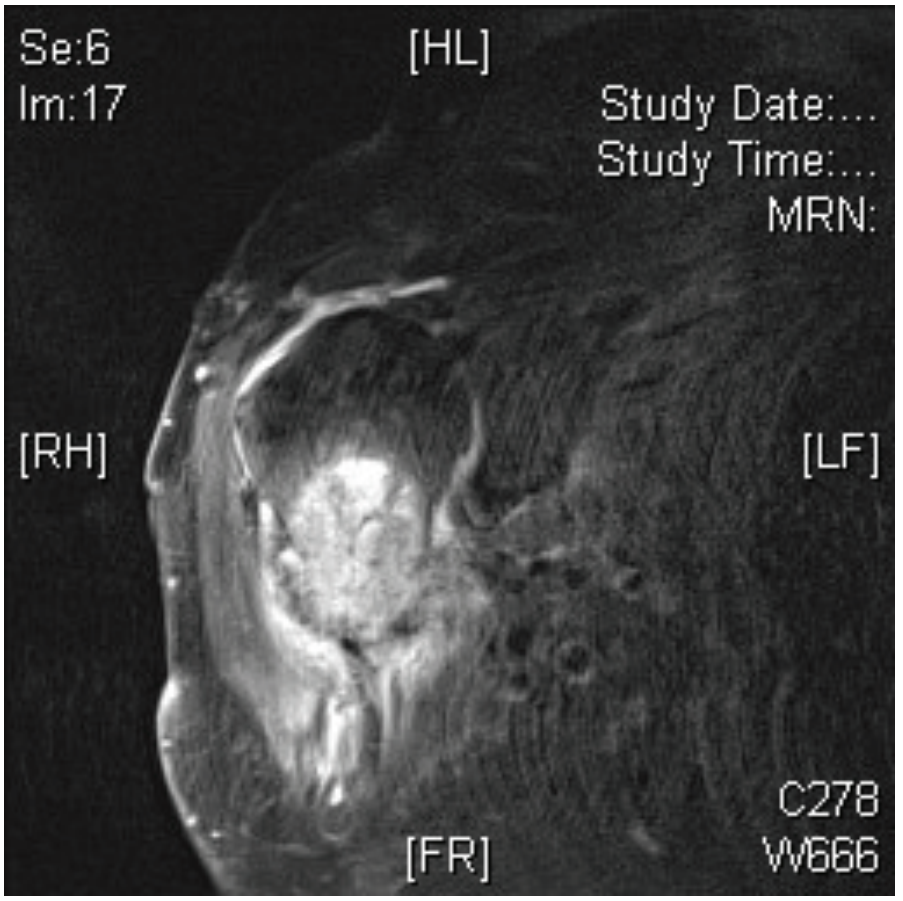

Figure 2. Magnetic resonance imaging STIR (short tau inversion recovery) in coronal plane shows predominant high signal intensity in neck of humerus associated with infiltrative lytic lesion extending to soft tissues and edema, measuring 5.5 cm.

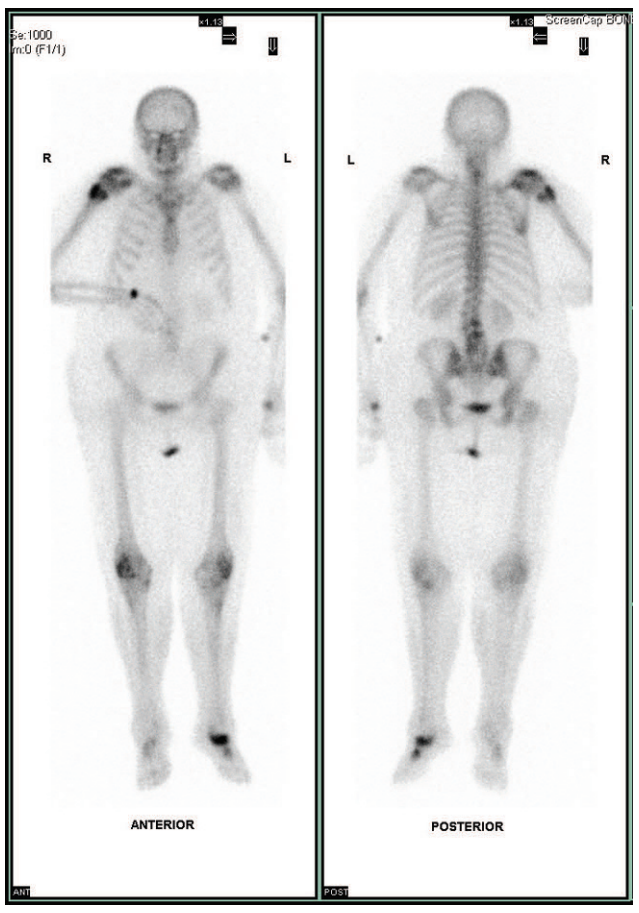

Figure 3. Whole body nuclear scan confirms uptake in base of coracoid process and proximal humerus but refutes widespread bone metastases.

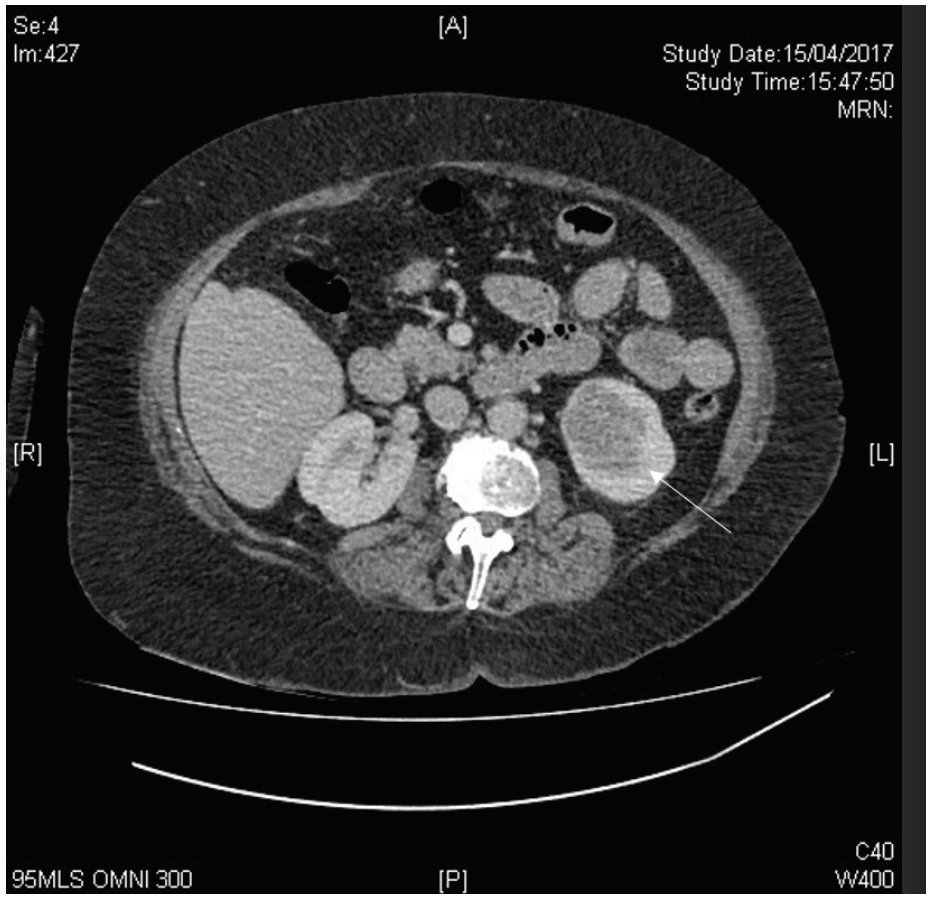

Figure 4. CT abdomen, in axial plane at renal level, shows heterogeneously enhancing mass at lower pole of left kidney (arrow), measuring 4 cm. No evidence of abnormal retroperitoneal lymphadenopathy.

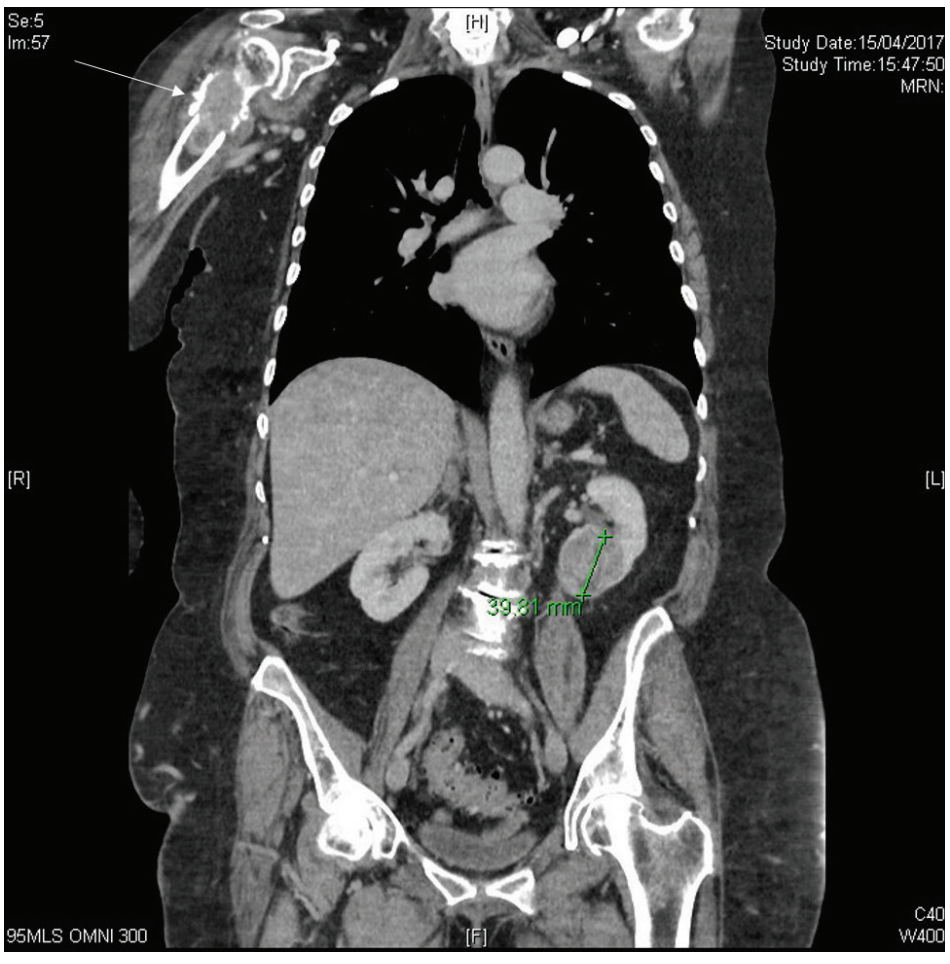

Figure 5. CT coronal plane shows primary heterogeneous mass measuring 4 cm with features suggestive of RCC in lower pole of left kidney and lytic lesion with bone fracture (arrow) in metaphysis of right humerus.

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Origin of Solitary Bone Metastases

▼ Continued from page 10

nephrectomy. Histopathology report of the excised left kidney showed a pT1aN0M0, Fuhrman grade 2, clear cell RCC with negative surgical margins. Renal function after nephrectomy has been stable at a baseline estimated glomerular filtration rate of around 50 ml per minute and she remains asymptomatic. She was reviewed by the oncology team and remains recurrence-free at 9 months of clinical and radiological followup.

Discussion

Solitary bone metastasis from an unknown primary RCC is a rare and atypical presentation of RCC. Such lesions are often large and generally part of a picture of disseminated disease.[1]

Few cases of solitary bone metastases from an unknown primary RCC have been published within the last few years.[2,3] What differentiates those published cases from ours is the stage and grade of the primary RCC, as in our case it was a mere T1a tumor with no aggressive features on histology while the size of the bone metastatic lesion was larger than the primary kidney tumor. Our results indicate that wide surgical excision of a solitary bony metastasis from renal cell carcinoma is not mandatory to improve survival. However, because 3 of 20 patients (15%) treated with stabilization alone had local disease progression, wide resection of metastatic lesions and stabilization may be necessary to prevent local disease progression and complications.[1]

Patients with solitary bone metastasis from RCC reportedly have the best prognosis with a 5-year survival rate between 35% and 60%. Due to the longer survival of patients with solitary bone metastasis, several investigators recommend an aggressive surgical approach with curative intent to prevent local disease progression.[4]

In metastatic disease the median survival rate is about 8 months with a 50% mortality rate within the first year, and the 5-year survival rate is 10%. Skeletal metastases are destructive in patients with renal cell carcinoma, compromising bone integrity and leading to skeletal related events including pain, impending fractures, nerve compression, hypercalcemia and even pathological fractures that may require surgical intervention and other therapy.

In addition to skeletal complications, the presence of bone metastases in RCC has a negative impact on progression-free and overall survival of patients treated with systemic therapies.[5] Even with limited followup we can conclude that in our experience the surgical excision of solitary metastasis may improve survival. ◆

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Transperineal Biopsy—Should We All Make the Change?

The Rise of the Perineum: TREXIT for the People

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The current gold standard for the diagnosis of prostate cancer is a 12-core transrectal ultrasound guided biopsy (TRUS), which is hardly a controversial statement in the United States. While this technique has been widely adopted, it is mired with multiple procedure related complications. With broad international data emerging almost weekly, the transperineal biopsy (TP) approach is proving to be a more promising alternative.

Before the adoption of a new method for cancer diagnosis, it must be at a minimum equal to the gold standard. At this time data suggest TP is equivalent to TRUS. Numerous studies have shown comparable cancer detection rates between TRUS and TP. A recent meta-analysis and systematic review included 13 studies (4,280 patients) and found no significant difference in detection rates of prostate cancer between the 2 methods.[1] As the use of multiparametric magnetic resonance imaging increases, obtaining fewer biopsy cores to diagnose clinically significant cancer is becoming far more important.

A recent study presented at the 2019 AUA annual meeting randomized 76 patients to transrectal and transperineal fusion biopsies.[2] The transperineal approach detected the index lesion more often than the transrectal approach (58% vs 44%). Additionally, the transperineal approach was superior in diagnosing cancer in the apex and anterior zones, which is particularly significant given that 20% to 30% of cancers are located in the anterior zone and are often missed.[3] While additional data are still needed to confirm the superiority of one method vs the other for the detection of clinically significant cancer, current evidence suggests comparable diagnostic accuracy.

Given the equivalency of these methods, the preferred approach should be the one that reduces harm to the patient. The primary morbidity associated with transrectal biopsy is infectious complications. Current estimates suggest that TRUS is associated with a 5% to 7% rate of infection and up to a 3% rate of sepsis requiring hospitalization.[4]

A recent series examined 1,287 consecutive patients who underwent TP biopsy with a single dose oral cephalosporin administered 2 hours before biopsy for the majority of the patients.[5] Overall 1.6% of patients experienced temporary urinary retention and 0.3% had lower urinary tract symptoms, with only 1 having a positive urine culture. Most importantly there were no episodes of sepsis. Only 1 patient was hospitalized in this series for post-biopsy hypotension.

The results of this study are in accordance with those of prior studies, all of which report near zero rates of infectious complications, although contemporary high quality randomized trials are lacking (see table).[5-15] As the antibiotic resistance of the rectal flora increases in the community, the transperineal approach is more appealing because it avoids the rectum and minimizes unnecessary broad spectrum antibiotic exposure.

Current literature suggests the transperineal technique is as accurate as transrectal biopsy and less morbid. The next relevant issues to address are the ease of clinical implementation and the cost-effectiveness of the transperineal approach. The previously mentioned study by Stefanova et al showed the feasibility of TP biopsy after its use in 1,287 patients using freehand technique with local anesthesia, with minimal patient reported discomfort (pain scores less than 3/10).[5] The authors commented that a small cohort of patients who underwent TRUS and TP reported no difference in discomfort level between the 2 procedures. Furthermore, after a 4 to 6-week learning curve the time to perform the biopsy was only 11 minutes, suggesting clinical feasibility.

Claims data of patients hospitalized for post-biopsy sepsis show a mean hospitalization cost of roughly 14,500 US dollars.[16] When extrapolated to the male Medicare population these complications yield an estimated cost of $623 million per year. While a 3% sepsis complication rate after TRUS seems low, this 3% is costing the system hundreds of millions of dollars per year. A 0% complication rate should be the goal and the transperineal approach can help accomplish this.

While England's Brexit may invite controversy, the British transrectalEXIT (TREXIT) movement should not. The UK National Health Service (NHS), a system of public health care providers, has set forth an initiative to transition completely to perineal prostate biopsy. Following their feasibility study the NHS has completely transitioned their South East London network to TP and intends to do the same across the country. They have implemented a collaborative approach in which urology nurses have an integral role by leading onsite training courses and formally installing local anesthesia TP biopsy in clinics throughout the UK.[17]

If we too can arrive at a consensus, we may begin to expunge TRUS biopsies as they have. The transperineal approach offers similar diagnostic accuracy with the potential for

▼ Continued on page 14

Table. Relevant studies examining cancer detection rates and post-biopsy complications for transrectal and transperineal prostate biopsies

References	No.	Pt Age	Ca Detection Rate (%)	Infection (%)	Other Complications (%)*
Stefanova et al[5]	1,287	66	49.8	0.3	1.60
Grummet et al[6, †]	245	61-70	39	0	Not reported
Meyer et al[7, †]	43	44-73	48.8	0	7
Huang et al:[8]					
TP:	130	66.6 ± 8.81	45	0	10.50
TRUS:	108	67.1 ± 8.45	49	7.4	31.30
Young et al:[9]					
TP	417	39-90	Not reported	0.48	6.95
TRUS	276	41-91	Not reported	0.36	4.18
Pepdjonovic et al[10, †]	577	60-70	Not reported	0	1.4
Merrick et al[11, †]	46	64.5 ± 10.0	67.4	0	Not reported
Di Franco et al:[12]					
TP	111	61-73	26.13	0	4
TRUS	108	58.5-70.5	34.26	2.30	8.700
Guo et al:[13]					
TP	173	67.18 ± 6.76	35.3	0	45.50
TRUS	166	7.35 ± 7.28	31.9	1.80	43.40
Cerruto et al:[14]					
TP	54	66.5 ± 8.9	21.43	0	12.96
TRUS	54	67.3 ± 8.1	16.79	1.80	11.11
Hara et al:[15]					
TP	126	71 ± 7.3	42.1	0	13.50
TRUS	120	71.7 ± 7.6	48.3	1.70	13.40

*Including urinary retention, gross hematuria, vasovagal event, hematospermia.
†Data on TP only.

Transperineal Biopsy
▼ Continued from page 13

improved apical/anterior cancer detection, eliminates infectious complications, could save millions of dollars in health care spending, and can be implemented into clinical workflow without much difficulty. So why not TREXIT?

Transperineal Biopsy: The Con Position

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Davis, California

During the last decade there has been increasing international interest in performing transperineal ultrasound guided prostate biopsy. Colleagues in the United Kingdom facetiously refer to their attempt at "TREXIT" to eliminate the use of the transrectal approach altogether.

The principal argument favoring the transperineal approach centers on the reported increase in infectious complications with the transrectal approach including sepsis and death. This is coincident with the rising prevalence of multidrug resistant bacteria in the community. Although I agree that there are some clear advantages to the perineal over the transrectal approach, it is neither ready nor necessary for prime time adoption.

An AUA white paper on the subject lists infectious complication rates after TRUS guided biopsy ranging from 0.1% to 7%.[4] These figures were obtained from studies including data up to 2010. A more recent systematic review of global data up to 2015 lists complications requiring hospitalization after transrectal biopsy of 1.1% (0-3.3) and sepsis in 0.8% (0-3).[18] These figures are in line with our contemporary experiences at the University of California, Davis with guideline based preventive measures. While transperineal approaches offer a lower risk of infections for obvious reasons, in reality the absolute differences are small and transrectal prostate biopsy remains a safe, high throughput office based procedure.

Infectious complications after TRUS biopsy are variable and easily limited with certain maneuvers. Recent recommendations from the AUA stress single dose, dual antibiotic prophylaxis based on knowledge of previous antibiotic exposures and local rectal flora antibiotic resistance patterns. Along with cleansing of the rectal vault with enema or povodine-iodine preparations, this can dramatically reduce the risk of significant post-biopsy infections.[4] Performed well with proper knowledge of local antibiograms, transrectal prostate biopsy remains a well tolerated and safe procedure with which most urologists are trained and comfortable.

The transperineal approach is not without complications as up to 1.6% of men experience acute urinary retention. Although infectious complication rates are low, patients still are given prophylactic antibiotics.[5] Increased patient discomfort and motion in the lithotomy position may also complicate multiparametric magnetic resonance imaging/ultrasound co-registration for software based fusion biopsy of target lesions. Many centers have extensive experience with the transperineal approach and describe methods for providing adequate local anesthesia, but there clearly is a learning curve.[19]

For transperineal ultrasound guided prostate biopsy to become the standard approach it must be successfully office based and performed using local anesthesia. Requiring anything more than this will increase patient risks and costs for an already financially strapped U.S. health care system. Regardless of approach, prostate biopsy should be performed well, in carefully selected men by experienced hands. ◆

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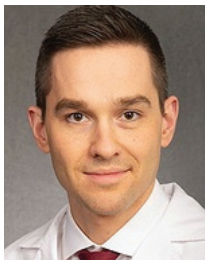
Treating Post-Radical Prostatectomy Erectile Dysfunction and Climacturia—Are We Asking the Right Questions?



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Climacturia refers to leakage of urine during sexual arousal, activity or orgasm and has been reported after radical prostatectomy in 28% to 93% of men. Interestingly, 10% to 37% of patients without stress urinary incontinence after prostatectomy report major bother from incontinence during sex.[1]

These numbers may seem staggering to prostate cancer surgeons unaccustomed to inquiring about incontinence during or preceding sexual activity. Understandably based on historical training paradigms, the urology community as a whole has generally limited the discussion of post-prostatectomy cancer survivorship to the topics of stress urinary incontinence and erectile dysfunction (ED).

In addition to climacturia, numerous other sexual dysfunctions are also prevalent, including penile shortening, sensory changes and delayed, absent, blunted or painful orgasms. While mild climacturia may be considered trivial by some, its impact on avoidance of sexual activity and decreased sexual satisfaction for the patient and partner have been well documented.[1]

Many conservative measures have been used to treat these patients including pre-intercourse voiding, condoms, urethra compressing variable tension loops, pelvic floor muscle training and a number of pharmacological treatments, all with varying efficacy. The male urethral sling and artificial urinary sphincter placement have been used as definitive surgical options.

Given the frequent coincidence of ED in patients with climacturia or mild urinary incontinence, the mini-jupette technique was developed as an adjunctive procedure performed during inflatable penile prosthesis implantation.[2] This procedure entails application of a small piece of material (processed pericardium or polymeric mesh) between the corporotomies to apply compression to the bulbar urethra with increased compression applied when the device is inflated. This procedure acts to reduce climacturia during intercourse as well as minimize urinary incontinence at baseline.

Valenzuela et al recently published a modification of this technique known as the male urethral mini sling.[3] The central piece of Coloplast Virtue® mesh is applied before prosthesis insertion to the urethra more proximally and laterally than in the procedure described by Adrianne. This technique allows for a decreased risk of damage to the prosthesis cylinders during sling suturing and greater distribution of pressure over a broader surface area.

Both approaches have been confirmed to be safe and efficacious with our own data showing complete resolution of climacturia in 93% of patients and improvement in mild stress incontinence in 85%.[3,4] The mean number of pads per day in the stress incontinence cohort decreased from 1.4 to 0.4. Only 1 patient required explantation due to urethral erosion following prolonged Foley catheter placement. Our results were similar to those presented in the original series of Yafi et al.[2]

However, there are some intrinsic limitations to the current technique. Given the lack of a commercially available product designed specifically for this purpose, we used a sling designed for application to the male urethra by a perineal approach. This approach is associated with significant cost and material waste as only a small portion of the mesh is used. A smaller, less expensive mesh expressly designed for this purpose is needed.

As a more cost-effective alternative, Towe et al recently proposed the use of autologous rectus fascia in place of mesh,[5] but larger studies with long-term data comparing synthetic mesh to autologous tissue are needed before widespread adoption can take place.

As cancer survivorship and quality of life outcomes following radical cancer surgery continue to gain attention, we must continue to innovate and offer novel treatments for consequent sexual dysfunctions. The core of the mini-jupette's novelty is that it treats a historically unrecognized problem.

Without specific inquiry by urological oncologists, general urologists, sexual medicine experts and others, post-prostatectomy climacturia and other sexual dysfunctions are likely to continue to be ignored, and patients will continue to suffer in silence. The high rates of these conditions in the published literature indicate that we should by default assume them to be present, and ensure we are offering appropriate counseling regarding expectations and treatment options. ◆

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Sacral Neuromodulation and Magnetic Resonance Imaging—Are They Truly Incompatible?

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Sacral neuromodulation (SNM) is an established therapy for refractory urinary urgency and frequency, urgency incontinence, nonobstructive urinary retention and fecal incontinence. The implanted hardware consists of a pulse generator (battery) and a quadripolar lead that is deployed through the S3 sacral foramen. By stimulating the S3 sacral nerve root, neural pathways are modulated in a way that allows for more favorable bladder and/or bowel function. First approved by the FDA (U.S. Food and Drug Administration) in 1997, more than 300,000 patients have undergone implantation worldwide.

Historically, patients with older SNM systems were cautioned against undergoing magnetic resonance imaging (MRI). Indeed, there are 3 magnetic fields, including mechanical force and torque due to a static magnetic field, induced current on leads by a pulsed magnetic field, and current induced into the generator body by the radio frequency magnetic field, that could potentially result in local tissue injury due to heating or damage to the implanted devices. However, advances have been made and the most widely available contemporary system, InterStim II (Medtronic), is FDA approved for 1.5 Tesla MRI of the head.[1]

Patients with the anticipated need for frequent nonhead MRI studies, such as those with progressive neurological disorders, are often steered away from SNM device implantation despite the potential benefit that SNM may provide. Nonetheless, patients with implanted SNM devices often require MRI of other body sites.

A 2017 study suggested that as many as 5% of implants may require removal for MRI, most commonly due to orthopedic (48%) or neurological (29%) indications.[2] Interestingly, despite therapeutic efficacy in more than two-thirds of the patients, only 10% underwent reimplantation after MRI was performed.

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Sacral Neuromodulation and MRI

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Two findings were perhaps even more concerning. Only 76% of patients who underwent explantation specifically for MRI ultimately underwent MRI and MRI changed management in only 56% of those who underwent imaging. The authors cautioned that, given not all expected MRIs were performed and that many imaging studies did not change management, surgeons should request documentation of the clinical necessity of MRI as well as the logistical scheduling of the procedure before removal of functioning SNM devices.

There has been mounting support during the last decade that MRI below the neck may be safe even in patients with implanted SNM devices. Indeed, when using an accepted phantom model of radio frequency induced heating in human tissue, Quirouet et al found no clinically significant heating with lumbar and pelvic 1.5T MRI in intact devices.[3] Reassuringly, the same was found for fractured leads.

In addition, an in vivo prospective trial was performed with 11 patients using intact SNM devices undergoing lumbosacral 1.5T MRI.[4] Two patients reported warmth at the implantable pulse generator site with 1 stating that it was slightly uncomfortable. The warmth subsided promptly following the MRI and no other patients reported symptoms. There were no major changes in impedance or battery life after MRI. Stimulus amplitude sensory thresholds and stimulation localization were unchanged. Validated questionnaires 1 month after imaging did not show worsening scores compared to scores before imaging.

While a growing body of literature suggests that MRI of below the neck sites may be safe with SNM devices in situ, it remains difficult to find a radiologist who will allow this protocol deviation. As such, manufacturers are interested in achieving FDA approval for these studies. Axonics recently received FDA approval for a MRI conditional rechargeable SNM system, with more than 90% of patients experiencing clinically significant improvement in urinary urgency incontinence symptoms in their ARTISAN-SNM trial.[5] Medtronic anticipates having a MRI conditional device available within the next year.

Nonetheless, while new devices may allow greater latitude for MRI, hundreds of thousands of previously implanted devices will still carry warnings. Therefore, ongoing study is needed to further characterize MRI parameters that are at once safe while still providing adequate image quality and anatomical coverage without the need for protracted imaging duration. ◆

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RADIOLOGY *Corner*

Vesicovaginal Fistula Years after Retained Vaginal Cylinder

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Introduction

Vesicovaginal fistulas (VVFs) are the most common type of urinary tract fistulas in adult females.[1] In developing countries obstructed labor and in developed countries gynecological surgery account for approximately 97% of all VVF cases.[2] Other less common causes include radiation therapy and vaginal foreign bodies.[3] In this case we report the radiographic findings of a rare case with VVF discovered years after missed vaginal metal foreign body.

Case Discussion

A 35-year-old female presented with a several-year history of continuous incontinence, dysuria and lower abdominal discomfort. Past medical history was significant for recurrent urinary tract infections, sexual assault and substance abuse.

Pelvic examination revealed an impacted foreign body obliterating the vaginal vault along with vaginal urine leak. A pelvic x-ray showed a large calcific shadow at the center of the pelvis (fig. 1). Further imaging with noncontrast pelvic computerized tomography (CT) showed a large calcific foreign body filling the bladder and the vaginal cavities (fig. 2). Cystoscopy failed to visualize the bladder wall or the fistula because the stone was filling the bladder cavity.

Due to the size and solid nature of the foreign body, vaginal approach was not technically feasible. The patient underwent laparotomy and successful foreign body removal with VVF repair and omental flap interposition. She was found to have an 8×5 cm stone that casted the vaginal and bladder lumens, communicating through the fistula tract. The stone was broken to reveal the core/nidus which turned out to be a metal cylinder.

The patient had a smooth postoperative recovery until 2 weeks after surgery when she experienced unexplained postoperative abdominal pain. CT cystogram was obtained

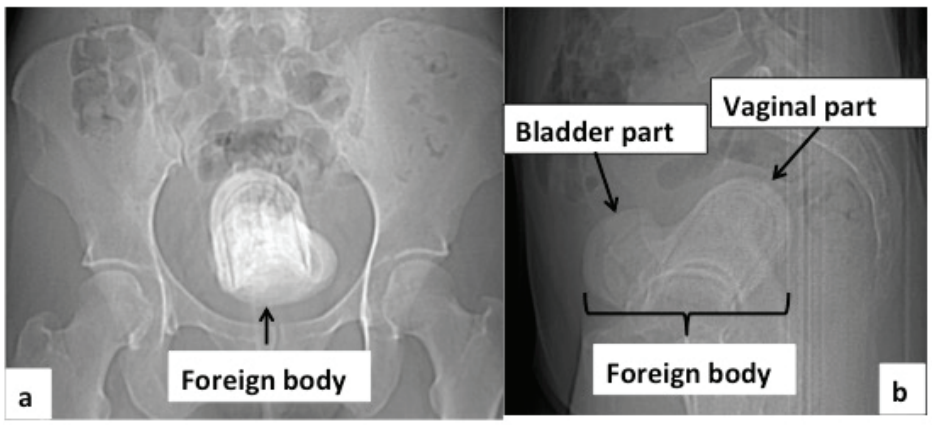

Figure 1. Anteroposterior (*a*) and lateral (*b*) pelvic x-ray views demonstrate large calcific shadow in center of pelvis.

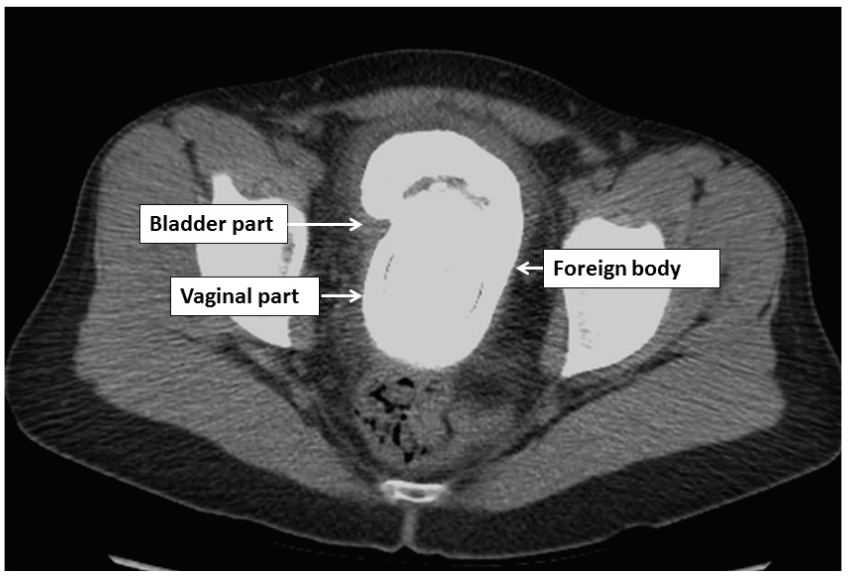

Figure 2. Cross section of CT of abdomen and pelvis demonstrates large calcific foreign body filling bladder and vaginal cavities.

and showed well closed fistulous tract with no contrast extravasation or evidence of fluid collection (fig. 3). The patient was treated conservatively and symptoms resolved. Catheter was removed 3 weeks after surgery.

The patient was lost to followup for a few months then came to the emergency department with lower abdominal pain. She denied urine incontinence at that time. Vaginal examination was negative for recurrent

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Erleada® (apalutamide) 60 mg tablets

Start early with ERLEADA®

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

NEW INDICATION

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

In the TITAN study† in patients with mCSPC:

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

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

INDICATION

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

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

ADVERSE REACTIONS

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

Laboratory Abnormalities—All Grades (Grade 3-4)

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

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

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

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

DRUG INTERACTIONS

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

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

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

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

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

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

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

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

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Brief Summary of Prescribing Information for ERLEADA® (apalutamide)

ERLEADA® (apalutamide) tablets, for oral use

See package insert for Full Prescribing Information

INDICATIONS AND USAGE

ERLEADA is indicated for the treatment of patients with

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Ischemic Cardiovascular Events

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

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

Fractures

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

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

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

Falls

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

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

Seizure

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

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

Embryo-Fetal Toxicity

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

ADVERSE REACTIONS

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

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

Clinical Trial Experience

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

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

Metastatic Castration-sensitive Prostate Cancer (mCSPC)

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

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

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

Table 1: Adverse Reactions in TITAN (mCSPC)

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

[1] Includes fatigue and asthenia

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

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

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

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

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

[1] Does not reflect fasting values

Non-metastatic Castration-resistant Prostate Cancer (nmCRPC)

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

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

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

Table 3: Adverse Reactions in SPARTAN (nmCRPC)

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

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

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

[1] Includes fatigue and asthenia

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

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

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

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

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

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

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

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

[1] Does not reflect fasting values

Rash

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

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

Hypothyroidism

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

DRUG INTERACTIONS

Effect of Other Drugs on ERLEADA

Strong CYP2C8 or CYP3A4 Inhibitors

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

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

Effect of ERLEADA on Other Drugs

CYP3A4, CYP2C9, CYP2C19 and UGT Substrates

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

P-gp, BCRP or OATP1B1 Substrates

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

Contraception

Males

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

Infertility

Males

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

Pediatric Use

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

Geriatric Use

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

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

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

OVERDOSAGE

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

PATIENT COUNSELING INFORMATION

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

Ischemic Cardiovascular Events

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

Falls and Fractures

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

Seizures

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

Rash

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

Dosage and Administration

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

Embryo-Fetal Toxicity

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

Infertility

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

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Radiology Corner

▼ Continued from page 16

fistula. Necessary evaluation for abdominal pain at the emergency room was negative and she was treated conservatively.

Conclusion

Missed vaginal foreign body is a well described, although rare, cause of VVF. A thorough diagnostic workup including physical examination, cystoscopy and radiologic imaging is pertinent to the diagnosis and surgical management of VVF. ◆

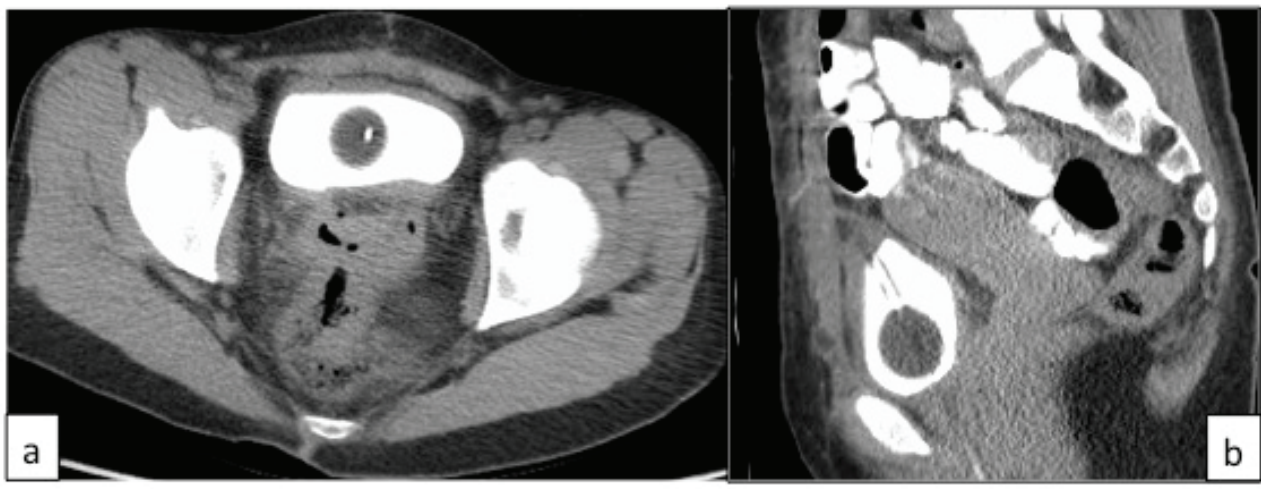

Figure 3. Cross section (*a*) and sagittal (*b*) views of CT cystogram show successful fistula closure.

1. D'Elia C, Curti P, Cerruto MA et al: Large urethro-vesico-vaginal fistula due to a vaginal foreign body in a 22-year-old woman: case report and literature review. Urol Int 2015; **95**: 120.
2. Radnia N, Eftekhar T, Sohbati S et al: Vesicovaginal fistula associated with a vaginal foreign body in a 16-year-old girl. Nephro-Urol Mon 2018; doi: 10.5812/numonthly.82387.
3. Bandarkar AN, Adeyiga AO and Shalaby-Rana E: Ureterovaginal fistula secondary to retained vaginal foreign body in a young girl. Radiol Case Rep 2017; **12**: 720.

Using Social Media for Patient Related Outcomes

Courtney K. Rowe, MD
Hartford, Connecticut

Have you used social media today? Your patients almost certainly have. An estimated 72% of Americans use some form of social media, with the majority of users visiting sites such as Facebook, Instagram and YouTube daily.[1] Social media refers to interactive, accessible, interconnected online platforms where users can share and create content.

The move from single author driven print media to user driven social media has mimicked the move in medical research from evaluating only physician driven outcomes to including a patient centered understanding of health. In this new era many have turned to social media as an efficient and cost-effective research tool.[2] After all, what better place to meet our patients for research into their outcomes and experiences than the social networks they helped create?

Social Media to Recruit Research Participants

The accessibility and connectivity of online social networks have been harnessed to inexpensively recruit, enroll and communicate with research subjects. Combined with web based surveys this approach is thought to improve responses, particularly for rare conditions that might be spread across geographic distances. The anonymity of online surveys may also increase honesty, especially about sensitive topics.

Researchers can reach participants using their own or their institution's social media channels, or with paid advertisements on networks such as Facebook. An alternative strategy is to recruit participants and pay them a small sum using a crowdsourcing marketplace such as the Amazon Mechanical Turk platform, which pays individuals small amounts of money to perform online tasks such as filling out surveys. Another valuable tool involves patient advocacy groups, which are often willing to harness their large social networks to help with research in an area they value (fig. 1.)

One limitation is that the denominator of eligible participants reached is unknown. Social media accounts are rarely followed by only the target population and posts can also be endlessly duplicated and forwarded. Other limitations include the need for patients recruited through social media to self-identify with a disease that is being researched and the inability to easily link responses to clinical data.

Social Media to Collect Data

The accessible nature of social media posts allows sites to be mined for content regarding patients' experiences. In this instance a social network is used in a similar manner to a patient focus group, but without the expense, time commitment and geographic constraints. Public postings on blogs or online message boards including Reddit can be reviewed for content through researcher review or digital methods such as natural language processing. Qualitative research methodology can then be used, and the results cataloged into themes to understand the concerns of that patient population (fig. 2.)

Unlike in a traditional patient focus group, data mining in social media offers no opportunity to ask for clarification or for followup questions, thus limiting its effectiveness. There are also concerns that social media discussions, even anonymous ones, may represent only a portion of patients and patient experiences, especially given that social media users tend to be younger than the general population.

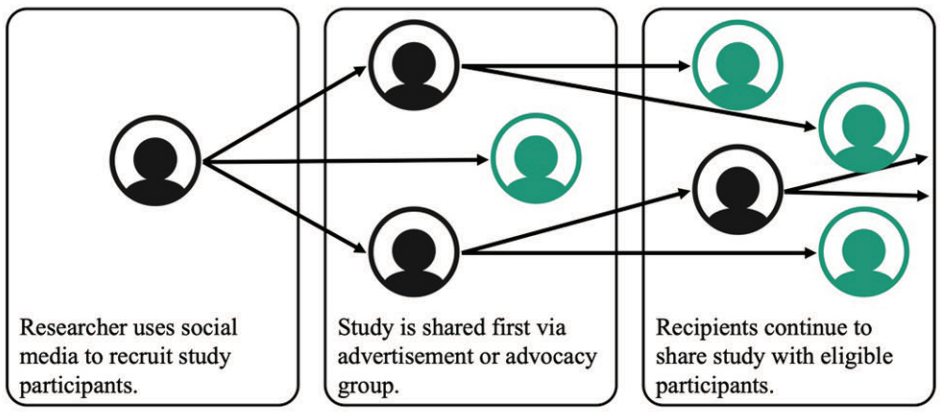

Figure 1. Social media to recruit and enroll research participants.

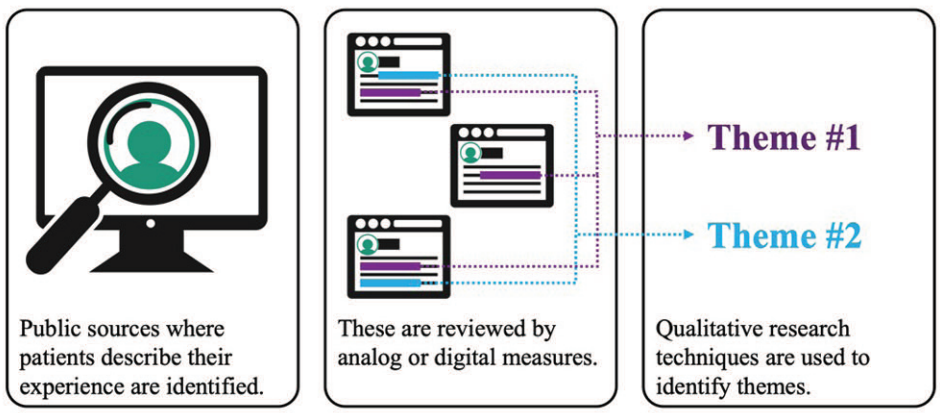

Figure 2. Social media to collect qualitative data on patient experience.

▼ Continued on page 22

HAVE YOU *Read?*

Daniel Shoskes, MD
Cleveland, Ohio

Oni OA, Dehkordi SHH, Jazayeri MA et al: Relation of testosterone normalization to mortality and myocardial infarction in men with previous myocardial infarction. Am J Cardiol 2019; 124: 1171-1178.

One of the many current recommendations about testosterone therapy is to avoid normalization in men shortly after a heart attack. Is this justified?

In this study the authors sought to determine the incidence of recurrent myocardial infarction (MI) and all-cause mortality in subjects with a history of MI and low total testosterone (TT) with and without testosterone replacement therapy (TRT). They retrospectively reviewed 1,470 cases of documented low TT levels and previous MI, categorized into Gp1—TRT with normalization of TT levels (755 cases), Gp2—TRT without normalization of TT levels (542) and Gp3— no TRT (173).

The association of TRT with all-cause mortality and recurrent MI was compared using propensity score weighted Cox proportional hazard models. All-cause mortality was lower in Gp1 vs Gp2 (HR 0.76, CI 0.64–0.90, p = 0.002) and in Gp1 vs Gp3 (HR 0.76, CI 0.60–0.98, p = 0.031).

There was no significant difference in the risk of death between Gp2 and Gp3 (HR 0.97, CI 0.76–1.24, p = 0.81). Adjusted regression analyses showed no significant differences in the risk of recurrent MI between groups (Gp1 and Gp3 HR 0.79, CI 0.12–5.27, p = 0.8; Gp1 and Gp2 HR 1.10, CI 0.25–4.77, p = 0.90; Gp2 and Gp3 HR 0.58, CI 0.08–4.06, p = 0.58).

The authors conclude that in a large observational cohort of male veterans with previous MI normalization of TT levels with TRT was associated with decreased all-cause mortality compared with those with non-normalized TT levels and the untreated group. Furthermore, in this high risk population TRT was not associated with an increased risk of recurrent MI.

Hu YY, Ellis RJ, Hewitt DB et al: Discrimination, abuse, harassment, and burnout in surgical residency training. N Engl J Med 2019; 381: 1741-1752.

As residency interview season begins (at the time of writing) it is important to reflect on the residency experience and look beyond "I went through it and it toughened me up, so let's not change anything" mentality.

The authors performed a cross-sectional national survey of general surgery residents administered with the 2018 American Board of Surgery In-Training Examination assessment of mistreatment, burnout (evaluated with the use of the modified Maslach Burnout Inventory) and suicidal thoughts during the past year. They used multivariable logistic-regression models to determine the association of mistreatment with burnout and suicidal thoughts. The survey asked residents to report their gender.

Among 7,409 residents (99.3% of those eligible) from all 262 surgical residency programs 31.9% reported discrimination based on their self-identified gender, 16.6% racial discrimination, 30.3% verbal and/or physical abuse and 10.3% sexual harassment. Rates of all mistreatment measures were higher among women, with 65.1% reporting gender discrimination and 19.9% reporting sexual harassment.

Patients and their families were the most frequent sources of gender discrimination (as reported by 43.6% of residents) and racial discrimination (47.4%), whereas attending surgeons were the most frequent sources of sexual harassment (27.2%) and abuse (51.9%). The proportion of residents reporting mistreatment varied considerably among residency programs (eg ranging from 0% to 66.7% for verbal abuse).

Weekly burnout symptoms were reported by 38.5% of residents, and 4.5% had suicidal thoughts during the past year. Residents who reported exposure to discrimination, abuse or harassment at least a few times per month were more likely than those not exposed to mistreatment to have symptoms of burnout (OR 2.94, 95% CI 2.58–3.36) and suicidal thoughts (OR 3.07, 95% CI 2.25–4.19).

Although models not adjusted for mistreatment showed that women vs men were more likely to report burnout symptoms (42.4% vs 35.9%, OR 1.33, 95% CI 1.20–1.48), the difference was no longer evident after the models were adjusted for mistreatment (OR 0.90, 95% CI 0.80–1.00).

Cohen JE, Yura EM, Chen L et al: Predictive utility of prior negative urine cultures in women with suspected recurrent uncomplicated urinary tract infections. J Urol 2019; 202: 979-985.

A great deal of antibiotic overuse in urology comes from treating the symptoms of a urinary tract infection (UTI) when no such infection exists. The authors note that guidelines recommend treating women who have symptoms of an uncomplicated UTI with antimicrobials without performing a urine culture. However, culture is negative in 10% to 50% of women with UTI symptoms. Urinalysis data are useful to predict a negative culture.

The authors evaluated how a previous negative culture predicts the likelihood of a subsequent negative culture. They gathered retrospective data on women 18 years old or older with symptoms of an uncomplicated UTI who submitted urine cultures as outpatients from 2011 to 2017. Univariate analysis and multivariable regression models were used to determine the likelihood ratios and risk ratios of predicting a negative culture. Of the 20,759 patients 9,271 (44.7%) had a negative culture, defined as less than 10^3 cfu/ml, and 6,958 (33.5%) had at least 1 prior culture, including 4,510 (64.8%) with at least 1 prior negative culture and 2,634 (58.4%) with a subsequent negative culture.

Variables associated with an increased likelihood of another negative culture were a prior negative culture (LR 1.43, 95% CI 1.387–1.475), prior negative culture and negative urinalysis (LR 1.839, 95% CI 1.768–1.913), and vaginal irritation and/or discharge (LR 1.335, 95% CI 1.249–1.427, each p <0.001). Urinalysis was 83% specific with a 78% positive predictive value. These values were significantly enhanced if the patient had a prior negative culture without a prior positive culture (specificity 95%, positive predictive value 87%).

The authors conclude that because women with recurrent UTI symptoms, and prior negative culture and urinalysis are highly likely to have another negative culture, they may benefit from further evaluation. ◆

Social Media for Patient Related Outcomes

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Researching Social Media Itself

The last area of research opportunity comes from understanding the patient experience when they use social media as a resource, which can be accomplished by surveying patients directly about their social media use and its impact on their health outcomes. It can also be done indirectly by accessing the same online references that patients would use and evaluating them for quality and accuracy.

The latter method is assisted by a number of tools, including the DISCERN score, which evaluates the quality of online health information (http://www.discern.org.uk/), the Patient Education Materials Assessment Tool (PEMAT) developed by the U.S. Department of Health and Human Services, which evaluates understandability and actionability (https://www.ahrq.gov/ncepcr/tools/self-mgmt/pemat.html), and the HON Code of Conduct, a set of ethical standards for online health information established by the nonprofit Health On the Net Foundation (www.hon.ch).

Ethical Concerns

As is often the case, new avenues for research raise new ethical concerns. Ethicists have questioned whether consent performed online is truly informed given the way users have been conditioned to "agree" to online contracts without reading them closely. There are also concerns that while social media posts are public, users may not fully understand the implications if their online actions are used for research purposes. This issue is illustrated by the Cambridge Analytica scandal in which research conducted using Facebook data overstepped expectations of privacy. While the actions of the companies do not seem to have broken U.S. law, the public outcry and resulting distrust in Facebook were significant.

Medical researchers exploring new territory with social media research should ensure that their projects are not only appropriate in terms of HIPAA (Health Insurance Portability and Accountability Act) security and institutional review board approval, but will also hold up to scrutiny from a lay public that is becoming increasingly concerned about online privacy.[3,4]

Conclusion

Social media offers a unique and increasingly appealing opportunity to reach patients directly and evaluate their health experience. Researchers considering this novel approach will find it an efficient and cost-effective manner to better understand patient related outcomes. ◆

1. Pew Research Center, Internet & Technology: Social Media Fact Sheet 2019. Available at https://www.pewresearch.org/internet/fact-sheet/social-media/. Accessed November 11, 2019.
2. Truong H, Salib A and Rowe C: The use of social media in pediatric urology – forging new paths or crossing boundaries? Curr Urol Rep 2019; **20**: 72.
3. Bhatia-Lin A, Roberts MK, Pronai C et al: Ethical and regulatory considerations for using social media platforms to locate and track research participants. Am J Bioeth 2019; **19**: 47.
4. Ferrigno BN and Sade RM: Ethics of recruiting research subjects through social media. Am J Bioeth 2019; **19**: 73.

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FROM THE *AUA Secretary*

Looking Forward to Seeing You in Washington, D.C. for AUA2020

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

Washington, D.C. is not only the best historical city to visit in the United States, but it is also home to the 115th AUA Annual Meeting from May 15–18, 2020 at the Walter E. Washington Convention Center.

The AUA annual meeting is the largest gathering of urologists in the world and it is where you will find unparalleled access to groundbreaking research, new guidelines and the latest advances in urological clinical care. Last year we welcomed more than 16,000 attendees from over 100 countries, underscoring the value of the meeting to the global urology community.

AUA's annual meeting as well as other year-round educational offerings provides the highest standards for urological education. AUA programs offer something for everyone, including residents, researchers, medical students and others. The AUA2020 program will cover topics such as pain management for urological surgery, space exploration and urological health risks, genetic testing and behavioral economics applications in urology. There are also educational offerings tailored for advanced practice providers and practice managers.

New this year is "Deferred Live Surgeries" which will include audience and moderator interaction.

As in previous years, soon-to-be released AUA clinical guidelines will be presented, the topics of which are premature ejaculation, asymptomatic microhematuria, advanced prostate cancer and male infertility. This year's program will also feature guest speaker Diana Nole, Chief Executive Officer of Wolters Kluwer Health, who will be discussing artificial intelligence and its impact on clinical care.

AUA's annual meeting continues to provide information about the newest advances in clinical care, as well as new surgical techniques, innovations, discoveries and technologies. With all the AUA has to offer, it is no wonder attendees unanimously state that the knowledge they receive at the meeting positively impacts their practices.

I am confident AUA2020 will exceed your expectations as we expand, perfect and introduce fresh and innovative offerings into our overall scientific program. Our goal is to provide high quality, dynamic sessions of only the best of the best.

While in Washington, D.C., please enjoy the rich history and many historical monuments, walk through the famous museums and take in a Washington Nationals baseball game. There are plenty of sights to see and more than 2,200 great restaurants.

The AUA2020 Annual Meeting registration site is now open. I encourage you to visit www.AUA2020.org and take advantage of the extended early bird discount period and reserve your housing as well.

See you in Washington, D.C.! ◆

Advocating for a National Office of Men's Health

Christopher Gonzalez, MD, MBA
Chair, AUA Public Policy Council
Chicago, Illinois

Jason Jameson, MD
SMSNA Legislative Affairs Committee
Phoenix, Arizona

Advocating for men's health continues to be a priority for many stakeholders, including organized medicine and patient advocacy groups. Urologists are the obvious champions of common conditions unique to men such as prostate cancer, prostate disease and erectile dysfunction. In addition, male infertility is a marker of overall health, and erectile dysfunction is associated with underlying diseases that are more prevalent in men, including cardiovascular disease and stroke. Erectile dysfunction is even correlated with all cause mortality.

During the last decade men have shown poorer health outcomes than women across all racial and ethnic groups as well as socioeconomic status. Risks to their health and well-being are on the rise due to a lack of education on, awareness of and pursuit of preventive screening and care.

Men are leading in 9 of the top 10 causes of death and die at an overall rate of 1.4 times higher than women. Studies show that women are 100% more likely than men to visit a doctor, have regular physician checkups and obtain preventive screening tests for serious diseases. Appropriate use of tests such as prostate cancer screening examinations, and blood pressure, blood sugar, lipid panel and colorectal screenings in conjunction with clinical examinations or self-testing can result in the early detection of many problems and increased survival rates. Common urological conditions impacting men would benefit from improved coordination of public awareness and screening programs.

Given the life expectancy gap between men and women, currently approximately 5 years shorter for American men, the call for a federal Office of Men's Health continues to grow with the hopes of replicating the success of the Office of Women's Health that was established in 1991, resulting in much needed advances in the nation's approach to women's health research, awareness, education and care. The ultimate goal is to equally improve men's and women's health, which is so critical to overall family health.

At the 2018 Annual Urology Advocacy Summit specialty societies were given the opportunity to highlight their respective advocacy priorities. The SMSNA (Sexual Medicine Society of North America) chose men's health as their featured topic and invited Ana Fadich, MPH, Vice President of Men's Health Network™, to discuss the legislative environment to create an Office of Men's Health within the U.S. Department of Health and Human Services.

In fact, the AUA chose this legislative issue as one of their main "asks" when summit attendees made visits to Capitol Hill to meet with their respective lawmakers. As most legislation takes years to develop, Men's Health Network and AUA Legislative and Political Affairs staff continue to pursue this goal, seeking support from legislators such as those on the Congressional Men's Health Caucus, co-chaired by Reps. Donald Payne, Jr. (D-NJ-10) and Markwayne Mullin (R-OK-02).

An Office of Men's Health would conduct, support, coordinate and promote programs and activities to improve the state of male health in the United States. Such an office would 1) coordinate public awareness, programs and activities related to male health, including prostate cancer, diabetes, colorectal cancer, cholesterol and mental health screening programs; 2) support comparative effectiveness review related to these diseases; and 3) establish a clinical registry to assess and measure quality improvement of programs and activities relating to male health.

As the movement for men's health advocacy grows, the AUA will continue to reach out to other stakeholders, maintain the collaboration with specialty societies and coordinate the message of urology so our voices can be heard loud and clear in Washington. ◆

FROM THE *AUA Research Council*

Engaging Patient Advocacy Groups for Success in Clinical Trials

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

Clinical trials are vital for improving our knowledge and advancing the care for our patients. While urologists have the appropriate knowledge to devise a clinically relevant question, patient recruitment is often one of the biggest barriers to conducting a clinical trial.

Some of the most challenging aspects of recruitment are inherent to specific patient populations. For example, enrollment of patients for the study of rare diseases is hindered by the difficulties in identifying these individuals. Cystinuria, for instance, is an autosomal recessive, inherited metabolic disorder that affects transepithelial transport of cysteine and dibasic amino acids across the intestine and kidneys, and leads to formation of renal calculi. Renal failure will develop in untreated patients, and any new pharmacological advances to manage this disease are met with difficult patient accrual into a clinical study.

Likewise, but even more pervasive, African Americans are underrepresented in clinical trials partly because of the mistrust they have in the medical system. The Tuskegee study conducted by the U.S. government from 1932 to 1972 excluded African American sharecroppers with syphilis from being treated without their consent, resulting in continued distrust of the medical research establishment in the African American community.

Clinical trial recruitment of populations with specific disease conditions associated with common urological diseases like prostate, kidney and bladder cancer, and interstitial cystitis can also be a challenge. For example, accrual of patients to assess efficacy of neoadjuvant vs adjuvant kidney cancer trials has been difficult particularly given the numerous targeted therapies that are currently available and the competition among different treatment options.

An often underused resource for our clinical researchers is patient advocacy groups. Groups like BCAN (Bladder Cancer Advocacy Network), KCCure (Kidney Cancer Research Alliance), PHEN (Prostate Health Education Network), ICA (Interstitial Cystitis Association) and NORD (National Organization of Rare Disorders) can significantly facilitate enrollment in clinical trials. Before designing a clinical trial patient engagement with the help of the advocacy groups will lead to better study design. These groups work closely with patients and establish trust, and these relationships are often a vital part of guiding the patients through treatment.

Moreover, with the help of patient advocacy groups patients are better prepared to learn about the research process, which can lead to better engagement in clinical trials. While clinical trials may seem like "inadequate and unproven" treatment to some patients, advocacy groups can better inform them about the risks and potential benefits of participation. Often, these groups help remove barriers for participation simply with the use of lay language, which leads to a better understanding and hopefully higher likelihood of patient participation. Through newsletters, webinars and face-to-face meetings, advocacy groups are a trusted and vital resource for many of our patients and their loved ones.

In addition to informing the patients about clinical trials advocacy groups also play an important role in educating the clinician researchers about considering not only the patient, but also their caregivers and living environment, all of which lead to better clinical trial design and higher likelihood of engagement. As consumers, patients deserve to be included in treatment strategies that affect their health, and as researchers we should listen more to our patients for design of clinical trials. Advocacy groups are outstanding partners to help us achieve those goals. ◆

Acknowledgements: I am grateful to Ms. Nicki Melhall (ICA), Dr. Stephanie Chisholm (BCAN), Mr. Thomas Farrington (PHEN) and Ms. Dena Battle (KCCure) for their time and insightful comments in preparing this editorial.

FROM THE *Chief Executive Officer*

Advancing Urology through Advocacy in 2020

Michael T. Sheppard, CPA, CAE
Linthicum, Maryland

In today's digital environment it is easy to forget the simple pleasure that a new calendar can bring as each new year brings new opportunities, challenges and goals. In the United States 2020 is not just a new year, but it is also an election year.

Advocacy is an important pillar of AUA's mission to promote the highest standards of urological clinical care, and there is no better time than an election year to celebrate and engage in the political process. As our members in the United States gear up for what promises to be an exciting November, the AUA has a number of ways for them to stand up for sound health policy by getting involved and bringing urology's policy priorities to lawmakers. How can you get involved?

Join AUA's Political Action Committee

Established in 2019 to further raise urology's profile and foster relationships with members of Congress, the American Urological Association Political Action Committee (AUAPAC) provides opportunities to engage lawmakers and strengthen our advocacy networks. Nonpartisan and representative of the voice and broad interests of our domestic members in the United States, AUAPAC had an exciting first year, contributing more than $20,000 to nearly 20 candidates, including the urologists in Congress, Dr. Neal Dunn (R-FL-2) and Dr. Greg Murphy (R-NC-3). You can learn more about AUAPAC by visiting www.myAUAPAC.org.

Share Your Voice and Become a Grassroots Advocate

No one understands how policy impacts practice better than physicians and their patients, and lawmakers want to hear from their constituents on legislation that impacts their districts. In the 116th Congress a number of bills have been introduced that impact the practice of urology, including the USPSTF (U.S. Preventive Services Task Force) Transparency & Accountability Act (H.R. 3534) and the Improving Seniors' Timely Access to Care Act of 2019 (H.R. 3107), an important bill to reform prior authorization in the Medicare Advantage program. Sending your letter is easy. Visit our action center at www.AUAnet.org/ActNow to get started.

Attend the 3rd Annual Urology Advocacy Summit

This spring, we will host our third AUA Summit in Washington, DC on March 16-18. Building on our highly successful 2018 and 2019 summits, this year's event will once again be inclusive of the entire urology community as our AUA sections, subspecialty societies and patient advocacy partners participate in this important event.

We are excited to welcome CBS Senior Foreign Affairs Correspondent and "Face the Nation" moderator Margaret Brennan as our keynote speaker at our opening luncheon on March 16. A veteran journalist who has been reporting on politics, international affairs and global markets for nearly 2 decades, Ms Brennan's news-making interviews and reporting have earned her a reputation as a tough but fair questioner with a wide range of expertise. She will kick off 3 days of advocacy education, meetings with lawmakers and agencies, and networking with colleagues. Whether you are a urologist, resident or fellow, an allied professional, researcher or patient, the Summit will have something for you. Register today at www.AUASummit.org.

For more information about our advocacy activities in 2020, please visit www.AUAnet.org or contact LegislativeAffairs@AUAnet.org. ◆

FROM THE *Urology Care Foundation*

Together, We Make a Difference

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

"We make a living by what we get, but we make a life by what we give."
—Winston Churchill

The Urology Care Foundation is the official foundation of the American Urological Association and is "your foundation." As such, it provides you with a profound opportunity to support urological research and education aimed at improving lives worldwide. In 2019 the Urology Care Foundation touched, directly or indirectly, the lives of millions of Americans with critical life-saving information through ambitious public awareness and education efforts. Additionally we provided millions of dollars to funding innovative research, advancing modern treatments and finding new cures to help the increasing number of men, women and children suffering from urological disease. I wish to highlight several important aspects of these efforts.

Research

The Foundation gave more than $1.5 million in research awards in 2019. These gifts not only fund the best research from talented scientists, but also help foster and support a long-lasting career to finding breakthroughs in patient care. This year's awards included 18 Research Scholars, 2 Residency Researchers, 1 Rising Stars in Urology Research and 14 Summer Medical Student Fellowship awards. All of these talented individuals are on course to become the future leaders in the field!

Patient Education

We are an international organization and as such, our focus is serving people from multiple countries, cultures and backgrounds who speak many different dialects. Therefore, this past year we translated 100+ patient education pieces and expanded our language offerings to include Brazilian Portuguese, Hindi, Italian, Punjabi and Spanish

To better meet the needs of your patients, we added more than 180 patient education resources to the library, including a new *Living Healthy: Fight Kidney Stones with Food* cookbook. Finally, we expanded our patient education library to include more than 300 free and credible resources by introducing over 50 podcasts and celebrating the release of our 100th podcast.

How did we do this? We were able to accomplish these initiatives because of the many individuals, organizations and corporate partners who generously gave their time, talents and financial support to further our crucial mission. In 2020 we plan to amplify our footprint worldwide by providing our materials in more languages. We also plan to release a second cookbook in our Living Healthy series and expand our compendium of patient resources, including our portfolio of podcasts, videos, assessment tools and patient guides that are current, medically approved and aligned with AUA clinical guidelines.

Our major donors have historically been the source of the Foundation's success today. The commitment and generosity of so many individuals have enabled us to plant the seeds to our growth while also helping to cultivate and attract other like-minded advocates and supporters who wish to be individuals who make a difference.

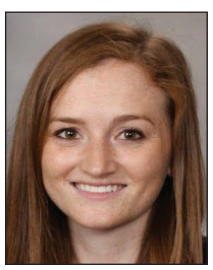
In recognition and appreciation to our major supporters, a new donor lifetime giving wall was created at AUA headquarters, which was unveiled in October 2019. The donor wall serves as a way to recognize, in perpetuity, as well as show our gratitude for our most generous individual and family Foundation donors. It is also a way to continue to remember and appreciate our donors and those who made a significant impact on the field of urology.

In the coming months you will see a series of articles highlighting those who have had a significant impact on urology and those who have benefitted by the support of the Urology Care Foundation. We invite you to visit the donor wall at AUA headquarters and to consider a major gift to the Foundation to help us continue to advance our research programs and expand our educational efforts worldwide.

We look forward to your support as we, together, strive to support and improve urological care by funding research and developing patient education. For more information on how to give, visit UrologyHealth.org/Donate. ◆

AUA RESIDENTS & FELLOWS *Committee News*

Making the Match



Margaret Knoedler, MD
North Central Section Representative, AUA Residents & Fellows Committee
Madison, Wisconsin

Sometimes we would go weeks without sharing a meal outside of the hospital. With one of us on day shift and one on nights, our only interactions were a brief kiss on the way out the door or at the threshold of the hospital.

When we started dating in medical school we thought we were busy but we were unprepared for just how busy our lives would become once we got to residency. My husband, Matt, started internal medicine residency at the same time I started urology, and despite the warnings from people who trod the path before us, we didn't really understand it until we experienced it. Being romantically involved with a resident is a tough proposition. Among the long stressful hours, sleep deprivation and endless pager messages, many aspects of residency do not lend themselves to a healthy relationship.

Can 2 residents make it work? I hope so, especially since we just had a baby. Fortunately, I do have some data on my side as 29% of male surgeons and 43% of female surgeons have physicians as domestic partners,[1] and so it's apparently doable. However, as we have discovered, you may need to readjust your expectations in certain areas.

Our house is a mess and gets cleaned as often as we can afford to pay someone to clean it. The lawn gets mowed sometimes. We can't make it to all the life events for friends and family. We have a live-in nanny and also pay for daycare. Some days our son goes a whole day without seeing me, which is the worst.

But for all the challenges, there are undeniable benefits to being in a relationship with another resident. There are the small things, like friendlier consults from your significant other's program and having 2 steady incomes. However, the most important benefit of having a resident as a partner is being with someone who understands some of the most important parts of you.

Medicine demands so much of us because it is tough and the stakes are high. For many of us being a physician is a big part of our identity. It's nice to come home to someone who understands why you stayed to help a patient or coworker even though you came home late. Someone who can understand the elation of doing a good job or the pain of knowing you made a decision that didn't turn out well.

That understanding is a fundamental part of our relationship. It makes it worth having a dirty house and lazy dinners for the time being. Like many before us, we have come to accept that you can't have it all but you can at least have what matters most. ◆

Margaret would like to thank Matthew Brunner for being an awesome husband and for editing this essay.

1. Dyrbye LN, Shanafelt TD, Balch CM et al: Relationship between work-home conflicts and burnout among American surgeons: a comparison by sex. Arch Surg 2011; **146**: 211.

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U.S.News & WORLD REPORT

NATIONAL UROLOGY 2019-20

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